Day : Tuesday
Date: 6/6/2006
Time: 19:58:42

PALM INTRANET

Inventor Information for 10/760639

Inventor Name	City	State/Country
DEMOPULOS, GREGORY A.	MERCER ISLAND	WASHINGTON
PALMER, PAMELA PIERCE	SAN FRANCISCO	CALIFORNIA
HERZ, JEFFREY M.	MILL CREEK	WASHINGTON

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | Inventors

Search Another: Application# [ ] Search **or Patent#** [ ] Search

PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

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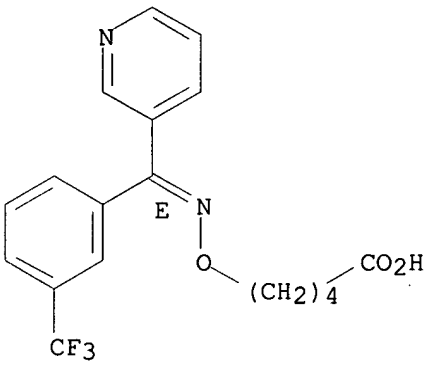
EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	"6645168".pn.	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:51
L2	1449	clopidogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:44
L3	282923	514/316.ccls.]	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:49
L4	587	l2 and l3	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:44
L5	124	l2 and l3	USPAT	OR	OFF	2006/06/06 19:44
L7	616	514/301.ccls.	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:47
L8	41	l7 and l2	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:47
L9	29	l3 and ridogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:48
L10	797	514/316.ccls.	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:49
L11	0	l10 and ridogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:49
L12	1963	514/317.ccls.	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:49
L13	3	l12 and ridogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:49
L14	1449	clopidogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:50
L15	141	ridogrel	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:51
L17	0	l14 and "l15"	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:51
L18	105	demopulos	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:51
L19	20	omeros and (clopidogrel or ridogrel)	US-PGPUB; USPAT	OR	OFF	2006/06/06 19:52

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 110140-89-1 REGISTRY
ED Entered STN: 05 Sep 1987
CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pentanoic acid, 5-[[[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]-, (E)-
OTHER NAMES:
CN R 68070
CN **Ridogrel**
FS STEREOSEARCH
DR 120950-49-4
MF C18 H17 F3 N2 O3
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

76 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
76 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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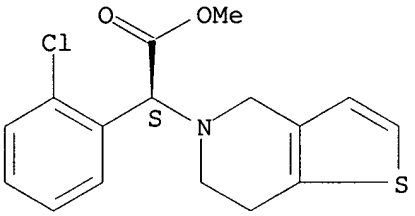
L1 ANSWER 12 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN 113665-84-2 REGISTRY
ED Entered STN: 02 Apr 1988
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)-
OTHER NAMES:
CN **(+)-(S)-Clopidogrel**
CN (S)-(+)-Methyl (2-chlorophenyl)(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate
CN **(S)-Clopidogrel**
CN (S)-Methyl α-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)-α-(o-chlorophenyl)acetate
CN **Clopidogrel**
CN SR 25990
FS STEREOSEARCH
MF C16 H16 Cl N O2 S
CI COM
SR World Health Organization (WHO)
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, EMBASE, IMSDRUGNEWS, IMSPATENTS, IPA, MRCK*, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

874 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
879 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

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TERMINAL (ENTER 1, 2, 3, OR ?):2

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NEWS 4	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS 5	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS 6	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS 7	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS 8	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS 9	MAR 22	EMBASE is now updated on a daily basis
NEWS 10	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 11	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS 12	APR 04	STN AnaVist $500 visualization usage credit offered
NEWS 13	APR 12	LINSPEC, learning database for INSPEC, reloaded and enhanced
NEWS 14	APR 12	Improved structure highlighting in FQHIT and QHIT display in MARPAT
NEWS 15	APR 12	Derwent World Patents Index to be reloaded and enhanced during second quarter; strategies may be affected
NEWS 16	MAY 10	CA/CAplus enhanced with 1900-1906 U.S. patent records
NEWS 17	MAY 11	KOREAPAT updates resume
NEWS 18	MAY 19	Derwent World Patents Index to be reloaded and enhanced
NEWS 19	MAY 30	IPC 8 Rolled-up Core codes added to CA/CAplus and USPATFULL/USPAT2
NEWS 20	MAY 30	The F-Term thesaurus is now available in CA/CAplus
NEWS 21	JUN 02	The first reclassification of IPC codes now complete in INPADOC
NEWS EXPRESS		FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT http://download.cas.org/express/v8.0-Discover/
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NEWS IPC8		For general information regarding STN implementation of IPC 8
NEWS X25		X.25 communication option no longer available after June 2006

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:16:40 ON 06 JUN 2006

=> file reg

COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION
FULL ESTIMATED COST | 0.21 | 0.21

FILE 'REGISTRY' ENTERED AT 10:16:51 ON 06 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 5 JUN 2006 HIGHEST RN 886840-90-0
DICTIONARY FILE UPDATES: 5 JUN 2006 HIGHEST RN 886840-90-0

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

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****
* The CA roles and document type information have been removed from the IDE default display format and the ED field has been added, effective March 20, 2005. A new display format, IDERL, is now available and contains the CA role and document type information. *
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/UG/regprops.html

=> s clopidogrel
L1 13 CLOPIDOGREL

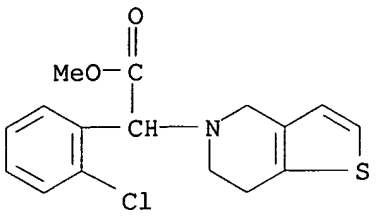
=> s ridogre
0 RIDOGRE
L2 0 RIDOGRE

=> s ridogrel
L3 1 RIDOGREL

=> d l1 13

L1 ANSWER 13 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN 90055-48-4 REGISTRY
ED Entered STN: 16 Nov 1984
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **(±)-Clopidogrel**
CN (±)-Methyl (2-chlorophenyl)(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate
CN (±)-Methyl α-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)-α-(o-chlorophenyl)acetate
CN Methyl 2-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)-2-(2-chlorophenyl)acetate
DR 120202-73-5, 94188-84-8
MF C16 H16 Cl N O2 S
CI COM

LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CHEMCATS, DDFU, DRUGU, EMBASE, IMSPATENTS, MEDLINE, PHAR, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)

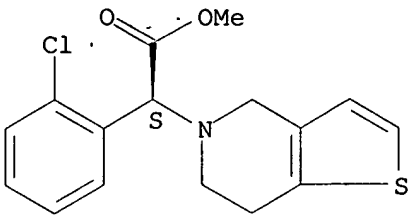
=> d l1 10-12

L1 ANSWER 10 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN 120202-66-6 REGISTRY
ED Entered STN: 21 Apr 1989
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)-, sulfate (1:1) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)-, sulfate (1:1)
OTHER NAMES:
CN (S)-(+)-Methyl (2-chlorophenyl)(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate bisulfate
CN (S)-(+)-Methyl 2-(2-chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetate hydrogen sulfate
CN **Clopidogrel bisulfate**
CN **Clopidogrel hemisulfate**
CN **Clopidogrel hydrogen sulfate**
CN Iscover
CN Methyl (S)-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)(2-chlorophenyl)ethanoate hydrogen sulfate
CN Plavix
CN SR 25990C
FS STEREOSEARCH
MF C16 H16 Cl N O2 S . H2 O4 S
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, EMBASE, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, PATDPASPC, PROMT, PROUSDDR, PS, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL

CM 1

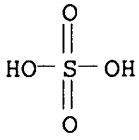
CRN 113665-84-2
CMF C16 H16 Cl N O2 S

Absolute stereochemistry. Rotation (+).



CM 2

CRN 7664-93-9
CMF H2 O4 S

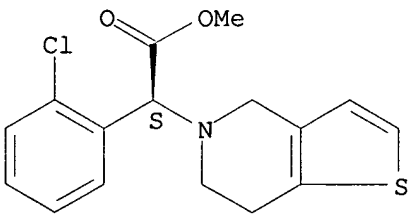


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

123 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
123 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 11 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN 120202-65-5 REGISTRY
ED Entered STN: 21 Apr 1989
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, hydrochloride, (αS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, hydrochloride, (S)-
OTHER NAMES:
CN **Clopidogrel hydrochloride**
FS STEREOSEARCH
MF C16 H16 Cl N O2 S . Cl H
SR CA
LC STN Files: CA, CAPLUS, IMSPATENTS, PROUSDDR, TOXCENTER, USPATFULL
CRN (113665-84-2)

Absolute stereochemistry. Rotation (+).



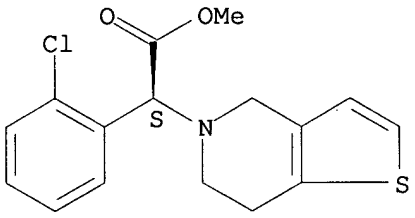
● HCl

12 REFERENCES IN FILE CA (1907 TO DATE)
12 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 12 OF 13 REGISTRY COPYRIGHT 2006 ACS on STN
RN 113665-84-2 REGISTRY
ED Entered STN: 02 Apr 1988

CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (S)-
OTHER NAMES:
CN **(+)-(S)-Clopidogrel**
CN (S)-(+)-Methyl (2-chlorophenyl)(6,7-dihydro-4H-thieno[3,2-c]pyrid-5-yl)acetate
CN **(S)-Clopidogrel**
CN (S)-Methyl α-(4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl)-α-(o-chlorophenyl)acetate
CN **Clopidogrel**
CN SR 25990
FS STEREOSEARCH
MF C16 H16 Cl N O2 S
CI COM
SR World Health Organization (WHO)
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, EMBASE, IMSDRUGNEWS, IMSPATENTS, IPA, MRCK*, PATDPASPC, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (+).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

874 REFERENCES IN FILE CA (1907 TO DATE)
10 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
879 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> d l2
L2 HAS NO ANSWERS
L2 0 SEA FILE=REGISTRY ABB=ON PLU=ON RIDOGRE

=> d his

(FILE 'HOME' ENTERED AT 10:16:40 ON 06 JUN 2006)

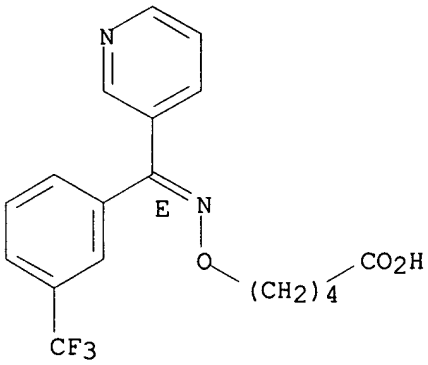
FILE 'REGISTRY' ENTERED AT 10:16:51 ON 06 JUN 2006
L1 13 S CLOPIDOGREL
L2 0 S RIDOGRE
L3 1 S RIDOGREL

=> d l3

L3 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2006 ACS on STN
RN 110140-89-1 REGISTRY
ED Entered STN: 05 Sep 1987
CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Pentanoic acid, 5-[[[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino

]oxy]-, (E)-
OTHER NAMES:
CN R 68070
CN **Ridogrel**
FS STEREOSEARCH
DR 120950-49-4
MF C18 H17 F3 N2 O3
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, SYNTHLINE, TOXCENTER, USAN, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

76 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
76 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus medline biosis embase

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	24.66	24.87

FILE 'CAPLUS' ENTERED AT 10:18:01 ON 06 JUN 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE 'MEDLINE' ENTERED AT 10:18:01 ON 06 JUN 2006

FILE 'BIOSIS' ENTERED AT 10:18:01 ON 06 JUN 2006

FILE 'EMBASE' ENTERED AT 10:18:01 ON 06 JUN 2006

=> s l1
L4 10762 L1

=> s l3
L5 494 L3

=> s l4 or clopidogrel
L6 11957 L4 OR CLOPIDOGREL

=> s l5 or ridogrel
L7 600 L5 OR RIDOGREL

=> s l6 and l7
L8 53 L6 AND L7

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 49 DUP REM L8 (4 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L9
L10 49 FOCUS L9 1-

=> d ibib abs hitstr 1-49

L10 ANSWER 1 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003121066 EMBASE
TITLE: **Clopidogrel** in prevention of cardiovascular events.
AUTHOR: Lowe G.D.O.
CORPORATE SOURCE: G.D.O. Lowe, University Department of Medicine, Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, United Kingdom
SOURCE: Reviews in Contemporary Pharmacotherapy, (2003) Vol. 12, No. 6, pp. 265-298. .
Refs: 209
ISSN: 0954-8602 CODEN: RCPHFW
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2003
Last Updated on STN: 3 Apr 2003

AB The risk of major cardiovascular events can be reduced by antiplatelet agents, an effect first demonstrated with acetylsalicylic acid (aspirin), which inhibits platelet cyclooxygenase, and more recently with thienopyridines, which produce their antiplatelet actions by inhibiting a platelet adenosine diphosphate receptor. Ticlopidine, the first thienopyridine to be shown to have clinically beneficial effects, also has an adverse effect profile which requires blood monitoring during the early stages of its administration; consequently, **clopidogrel**, a structural analogue of ticlopidine, has been examined in a number of large, randomized clinical trials involving patients with a high risk of cardiovascular events. In the CAPRIE trial, in patients with recent myocardial infarction, recent ischaemic stroke, or peripheral arterial disease, **clopidogrel** proved superior to aspirin in reducing the risk of the primary outcome (myocardial infarction, ischaemic stroke or cardiovascular death). This effect was subsequently confirmed by meta-analysis of all prospective comparisons between thienopyridines and aspirin. The CURE trial compared **clopidogrel** plus aspirin with aspirin alone in patients with acute coronary syndromes without ST elevation; **clopidogrel** plus aspirin was associated with a greater efficacy in reducing the primary outcome measure (myocardial infarction, stroke or cardiovascular death) than was seen with aspirin alone, a superiority seen within the first day of treatment. In the PCI-CURE trial, **clopidogrel** plus aspirin given over an extended period of time (3 months to 1 year) was more effective than a short, 4-week course of such treatment, in reducing the risk of cardiovascular death, myocardial infarction, or urgent target vessel revascularization within 30 days of percutaneous coronary intervention. In the CAPRIE trial, **clopidogrel** was found to be at least as safe as aspirin;

in the CURE and PCI-CURE tials, combined **clopidogrel** and aspirin treatment led to more bleeding complications than seen with aspirin alone, but these effects were generally minor. It is concluded that **clopidogrel** provides a useful alternative to aspirin in the secondary prevention of myocardial infarction and stroke in patients at high risk of cardiovascular events, and adds to the antithrombotic effect of aspirin in patients with acute coronary syndromes or undergoing percutaneous coronary interventions. Trials currently in progress will help to clarify further the clinical efficacy and adverse event profiles of **clopidogrel**, used either alone or in combination with aspirin.

L10 ANSWER 2 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 94168332 EMBASE
DOCUMENT NUMBER: 1994168332
TITLE: **Clopidogrel** and antiplatelet therapy.
AUTHOR: Herbert J.-M.
CORPORATE SOURCE: Haemobiology Research Department, Sanofi Recherche, 195 Route D'Espagne,31036 Toulouse Cedex, France
SOURCE: Expert Opinion on Investigational Drugs, (1994) Vol. 3, No. 5, pp. 449-455. .
ISSN: 0967-8298 CODEN: EOIDER
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jun 1994
Last Updated on STN: 29 Jun 1994

AB Large clinical trials performed with ticlopidine in patients with atherosclerotic arterial diseases showed that ticlopidine was of benefit to patients who were at high risk of vascular events and demonstrated that it was likely to be more efficacious than other antiplatelet drugs tested to date. The search for other active antiplatelet drugs within the original chemical class of the thienopyridines led to the discovery of a new molecule: **clopidogrel**. **Clopidogrel** is a novel ADP-selective agent whose antiaggregating properties are several times higher than those of ticlopidine and are apparently due to the same mechanism of action (inhibition of ADP binding to its platelet receptor). This effect has been seen in various experimental animal species as well as in healthy volunteers and in atherosclerotic patients. Of particular interest is the ability of this drug to prevent arterial as well as venous thrombosis in animals and also to reduce myointimal thickening occurring after endothelial injury of the rabbit carotid artery. **Clopidogrel** seems to be better tolerated than ticlopidine and, on the basis of the activity/toxicity ratio observed, appears to be a promising compound for evaluation in atherosclerotic cardiovascular and cerebrovascular diseases. The outcome of clinical trials currently in progress could provide definite evidence of **clopidogrel**'s efficacy.

L10 ANSWER 3 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003118822 EMBASE
TITLE: Current status of antiplatelet drugs in therapy.
AUTHOR: Arora D.; Kumar M.
CORPORATE SOURCE: Prof. D. Arora, Department of Pharmacology, Universal Coll. of Medical Sciences, Bhairahawa, Nepal
SOURCE: Journal of Internal Medicine of India, (2002) Vol. 5, No. 2, pp. 69-71. .
Refs: 11
ISSN: 0972-1096 CODEN: JIMIF8
COUNTRY: India

DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 2003
Last Updated on STN: 3 Apr 2003

AB The mortality and morbidity in arterial vascular diseases have been reduced greatly with use of low dose aspirin as antiplatelet drug. Many antiplatelet drugs have been introduced recently. The choice of the antiplatelet therapy in particular disease conditions is being determined and evidence is being available very fast. Aspirin remains the most preferred drug in patients with positive history of MI, unstable angina, stroke, TIAs and to reduce periprocedural thrombosis in percutaneous coronary angioplasty and saphenous vein graft. Comparative studies have suggested that ticlopidine and **clopidogrel** are also equally or slightly more effective in these conditions, however, aspirin has better safety profile. The different combinations of aspirin with other drugs are also giving encouraging results in these conditions. GPIIIa/IIb receptor antagonists have entered in clinical practice and are currently recommended as adjunctive therapy in the treatment of PCI and refractory unstable angina.

L10 ANSWER 4 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003079681 EMBASE
TITLE: The role of platelets and antiplatelet therapy in atherothrombotic disease.
AUTHOR: Goodall A.H.
CORPORATE SOURCE: Dr. A.H. Goodall, Department of Clinical Biochemistry, University of Leicester, Glenfield Hospital, Groby Road, Leicester LE3 9QP, United Kingdom. ahg5@le.ac.uk
SOURCE: British Journal of Cardiology, (2002) Vol. 9, No. SUPPL. 8, pp. S2-S7. .
Refs: 42
ISSN: 0969-6113 CODEN: BJCAEM
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 2003
Last Updated on STN: 6 Mar 2003

AB Platelet-initiated thrombus plays a central role in the pathogenesis of arterial thrombotic disease. Platelets are activated by a range of physiological agonists including thrombin, ADP, thromboxane and collagen, acting in co-operation. ADP, though a weak agonist on its own, is important in enhancing platelet activation induced by other agents. Activation results in platelet adhesion, aggregation and degranulation leading to thrombus growth. Platelets also reinforce thrombus formation through platelet-mediated thrombin generation and the release of PAI-1 that inhibits fibrinolysis. Antiplatelet therapy is therefore of potential benefit both prior to and during a thrombotic episode. The commonly used antiplatelet drugs inhibit specific, single pathways of platelet activation but have overall benefit. Inhibition of intracellular activation pathways can be achieved with aspirin (which inhibits platelet cyclo-oxygenase) and dipyridamole (which inhibits phosphodiesterase). Two related thienopyridine derivatives, ticlopidine and **clopidogrel**, are specific inhibitors of the P2Y(12) ADP receptor. They have comparable pharmacological activity but **clopidogrel** has a better safety profile. A number of potent glycoprotein IIb/IIIa antagonists have been

developed for therapeutic use. They are effective in percutaneous coronary intervention, though data from primary stenting trials are less positive. The recent update of the meta-analysis of trials of antiplatelet therapy by the Antithrombotic Trialists' Collaboration has confirmed the benefit of antiplatelet therapy in secondary prevention.

L10 ANSWER 5 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2005253835 EMBASE
TITLE: Platelets and new antiplatelet drugs.
AUTHOR: Reiter R.A.; Jilma B.
CORPORATE SOURCE: B. Jilma, Medical University of Vienna, Department of Clinical Pharmacology, Wahringer Gurtel 18-20, A-1090 Vienna, Austria. bernd.jilma@meduniwien.ac.at
SOURCE: Therapy, (2005) Vol. 2, No. 3, pp. 465-502. .
Refs: 340
ISSN: 1475-0708
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jun 2005
Last Updated on STN: 23 Jun 2005

AB Platelets play an important, life-saving role in hemostasis and blood clotting at sites of vascular injury. However, unwanted platelet activation and arterial thrombus formation are implicated in the onset of myocardial infarction, stroke and other cardiovascular diseases. Different mechanisms, such as vascular damage, the development of mural platelet thrombi as a response to injury and the biochemical effects of intraplatelet substances that are released in response to damage, may be involved. Thus, antiplatelet therapy has become a mainstay of treatment for these conditions and the benefit of antiplatelet drugs is documented across a wide spectrum of clinical conditions. Aspirin has been regarded as the prototype antiplatelet drug and is still the most widely used agent. Aspirin's antiplatelet effect is directly due to irreversible inactivation of arachidonic metabolism and suppression of thromboxane A(2) synthesis. However, platelet activation occurs via several pathways that do not rely on amplification by released thromboxane A(2). Therefore, a number of other compounds have been developed to complement the beneficial effect of aspirin. Four main classes of antiplatelet agents are currently available for clinical use: aspirin, phosphodiesterase inhibitors, thienopyridines and the platelet glycoprotein α(IIb)β(3) receptor antagonists. This review discusses state-of-the-art antiplatelet therapies and recent advances, using aspirin as the reference standard. .COPYRGT. 2005 Future Drugs Ltd.

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ACCESSION NUMBER: 1999390349 EMBASE
TITLE: Antiplatelet therapies: From aspirin to GPIIb/IIIa-receptor antagonists and beyond.
AUTHOR: Mousa S.A.
CORPORATE SOURCE: S.A. Mousa, DuPont Pharmaceuticals Co., Wilmington, DE 19880, United States. shaker.a.mousa@dupontpharma.com
SOURCE: Drug Discovery Today, (1999) Vol. 4, No. 12, pp. 552-561. .
Refs: 43
ISSN: 1359-6446 CODEN: DDTOFS
PUBLISHER IDENT.: S 1359-6446(99)01394-X
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology

037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Dec 1999
Last Updated on STN: 2 Dec 1999

AB This review discusses recent advances in antiplatelet therapies, comparative analysis between the antiplatelet/ antithrombotic efficacy of various antiplatelet strategies and that of platelet glycoprotein GPIIb/IIIa-receptor antagonists, issues in the development of chronic anti-GPIIb/IIIa-receptor therapy and potential adjunct strategies using GPIIb/IIIa-receptor antagonists. Acute coronary syndromes are secondary to unstable angina, ST-segment elevation, and acute myocardial infarction. These involve the rupture of a vulnerable atherosclerotic plaque, leading to platelet adhesion, activation and aggregation at the site of rupture. Several studies suggest that complex or ulcerated plaques, which might promote further thrombotic events, can persist for more than one month after the acute event. These data suggest the potential added benefit of chronic oral therapy with antiplatelet drugs beyond the well-documented benefit of acute intravenous use of various GPIIb/IIIa-receptor antagonists. However the efficacy-safety ratio or the risk-benefit ratio for chronic oral antiplatelet therapy needs to be defined. Both aspirin and **clopidogrel** are available for chronic oral use. By contrast, there are tremendous challenges ahead with the oral GPIIb/IIIa-receptor antagonists because of their lack of expected benefit over aspirin. However, much still remains to be defined with regard to the optimization of current and future antiplatelet therapies or their optimized combinations. Copyright (C) 1999 Elsevier Science Ltd.

L10 ANSWER 7 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003447981 EMBASE
TITLE: Scientific and therapeutic advances in antiplatelet therapy.
AUTHOR: Bhatt D.L.; Topol E.J.
CORPORATE SOURCE: D.L. Bhatt, Cleveland Clinic Foundation, Dept. of Cardiovascular Medicine, 9500 Euclid Avenue, Cleveland, OH 44195, United States. bhattd@ccf.org
SOURCE: Nature Reviews Drug Discovery, (2003) Vol. 2, No. 1, pp. 15-28. .
Refs: 173
ISSN: 1474-1776 CODEN: NRDDAG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 20 Nov 2003
Last Updated on STN: 20 Nov 2003

AB Over the past decade, the platelet has emerged as a pivotal entity in cardiovascular diseases. Indeed, the 'preeminence of the platelet' has spawned a variety of drugs that have been shown in large-scale randomized trials to improve patient outcomes in acute coronary syndromes and percutaneous revascularization procedures. Although the platelet was initially viewed only as a bystander in haemostasis, it is now evident that the platelet is in fact a key mediator of thrombosis as well as of inflammation. New insights at the cellular and genomic levels will probably generate novel drugs to inhibit platelet function more effectively and safely than previously possible.

L10 ANSWER 8 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002337857 EMBASE
TITLE: [Platelet aggregation inhibitors - Differential treatment in the doctor's office].
THROMBOZYTENAGGREGATIONSHEMMER IN DER PRAXIS: JEDER DRITTE INFARKT VERHUTET - REINFARKTRATE HALBIERT.

AUTHOR: Fliri M.
CORPORATE SOURCE: Dr. M. Fliri, Medizinische Klinik, Klinikum Augsburg, Postfach 101920, D-86009 Augsburg, Germany. mfliri@yahoo.de
SOURCE: MMW-Fortschritte der Medizin, (22 Aug 2002) Vol. 144, No. 33-34, pp. 38-41. .
ISSN: 1438-3276 CODEN: MFMEF8
COUNTRY: Germany
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: German
SUMMARY LANGUAGE: English; German
ENTRY DATE: Entered STN: 10 Oct 2002
Last Updated on STN: 10 Oct 2002

AB Depending on their mode of action, pharmaceuticals with an antithrombocytic effect are divided into five groups. In the doctor's office, acetylsalicylic acid (ASA) and the thienopyridines, such a ticlopidine and **clopidogrel** predominate. Acetylsalicylic acid should be considered for primary prevention in patients over 50 with a marked cardiovascular risk profile. In the secondary prophylaxis of myocardial infarction, life-long ASA treatment continues to be the treatment of choice. As an alternative, however, **clopidogrel** may be applied. A combination of acetylsalicylic acid and **clopidogrel** is recommended for patients who have been implanted with a stent. In patients with acute coronary syndrome, this regimen is superior to monotherapy with acetylsalicylic acid. In comparison with ticlopidine, **clopidogrel** has a more rapid onset of action, and has fewer side effects. In patients with an acute coronary syndrome and an elevated risk glycoprotein IIb/IIIa antagonists have proved highly effective.

L10 ANSWER 9 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001112159 EMBASE
TITLE: Platelet function inhibitors in the year 2000.
AUTHOR: Bennett J.S.; Mousa S.
CORPORATE SOURCE: Dr. J.S. Bennett, University of Pennsylvania, School of Medicine, Dept. of Med. Hemato-Onco-Division, 421 Curie Blvd., Philadelphia, PA 19104, United States. bennetts@mail.med.upenn.edu
SOURCE: Thrombosis and Haemostasis, (2001) Vol. 85, No. 3, pp. 395-400. .
Refs: 83
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
030 Pharmacology
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Apr 2001
Last Updated on STN: 12 Apr 2001
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 10 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003509706 EMBASE
TITLE: Advances in antiplatelet therapy.
AUTHOR: Jneid H.; Bhatt D.L.
CORPORATE SOURCE: Dr. D.L. Bhatt, Dept. of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, United States. bhattd@ccf.org
SOURCE: Expert Opinion on Emerging Drugs, (2003) Vol. 8, No. 2, pp. 349-363. .

Refs: 138
ISSN: 1472-8214 CODEN: EOEDA3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 017 Public Health, Social Medicine and Epidemiology
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Jan 2004
Last Updated on STN: 22 Jan 2004

AB Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality in the western world. These disorders share a common pathophysiology - atherosclerosis, which affects various arterial beds, leading to protean manifestations (coronary artery disease [CAD], stroke, peripheral arterial disease [PAD]). The platelet plays a pivotal role in the perpetuation and clinical expression of these disorders. The platelet, once believed to have a role confined to modulation of thrombosis and haemostasis, also plays an active role in vascular inflammation. Antiplatelet agents have become first-line therapy for CVD, and their unequivocal benefits are demonstrated in various basic and experimental models and supported by overwhelming evidence from clinical trials. Search is underway for more effective and safer antiplatelet therapy. Novel therapies are emerging to target the redundant pathways of platelet adhesion, activation and aggregation. Efforts are also ongoing to enhance implementation of existent therapy, target therapy selectively to high-risk patients and to those likely to respond (pharmacogenomics), and study the incremental benefits and safety of various antiplatelet combinations and their interaction with other medications in patients with CVD treated with polypharmacy.

L10 ANSWER 11 OF 49 EMBASE
ACCESSION NUMBER: 2005282548 EMBASE
TITLE: Blood platelet reactivity and its pharmacological modulation in (people with) diabetes mellitus.
AUTHOR: Watala C.
CORPORATE SOURCE: C. Watala, Department of Haemostasis and Haemostatic Disorders, Medical University of Lodz, 113 Zeromskiego Str., 90-549 Lodz, Poland. cwatala@csk.am.lodz.pl
SOURCE: Current Pharmaceutical Design, (2005) Vol. 11, No. 18, pp. 2331-2365. .
Refs: 369
ISSN: 1381-6128 CODEN: CPDEFP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jul 2005
Last Updated on STN: 14 Jul 2005

AB Blood platelets play a crucial role in physiological haemostasis and in pathology of prothrombotic states, including atherosclerosis. In this paper, we review major factors underlying altered platelet reactivity, with special attention paid to abnormalities in platelet function in people with diabetes mellitus (DM). The overall picture of platelet abnormalities in DM, including altered adhesion and aggregation, is hypersensitivity of diabetic platelets to agonists. "Primed" diabetic platelets respond more frequently even to subthreshold stimuli, sooner become exhausted, consumed and finally hyposensitive, thus contributing to accelerated thrombopoiesis and release of 'fresh' hyperreactive platelets. In diabetes disturbed carbohydrate and lipid metabolism may lead to

physicochemical changes in cell membrane dynamics, and consequently result in altered exposure of surface membrane receptors. These phenomena, together with increased fibrinogen binding, prostanoid metabolism, phosphoinositide turnover and calcium mobilisation often present in diabetic patients, contribute to enhanced risk of small vessel occlusions and accelerated development of atherothrombotic disease of coronary, cerebral and other vessels in diabetes. As platelet hypersensitivity in DM makes a major contribution to enhanced risk of thromboembolic macroangiopathy, and consequently enhanced morbidity and mortality, it validates use of antiplatelet agents in diabetic individuals. Platelet hyperreactivity may be cured with various antiplatelet drugs to a considerably large extent notwithstanding, evidence gathered from clinical and experimental surveys shows that this approach may not always be equally efficient in people with diabetes. Observations from clinical studies rather support the use of multifactorial strategy under such circumstances, like a combined therapy of aspirin plus either purinoreceptor blocker or GPIIb-IIIa antagonist.

L10 ANSWER 12 OF 49 EMBASE

ACCESSION NUMBER: 2004076238 EMBASE
TITLE: Platelets and anti-platelet therapy.
AUTHOR: McNicol A.; Israels S.J.
CORPORATE SOURCE: A. McNicol, Department of Oral Biology, University of Manitoba, Winnipeg, Man. R3E OW2, Canada. mcnicol@ms.umanitoba.ca
SOURCE: Journal of Pharmacological Sciences, (2003) Vol. 93, No. 4, pp. 381-396. .
Refs: 173
ISSN: 1347-8613 CODEN: JPSTGJ
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
030 Pharmacology
018 Cardiovascular Diseases and Cardiovascular Surgery
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 2004
Last Updated on STN: 26 Feb 2004

AB Platelets play a central role in the hemostatic process and consequently are similarly involved in the pathological counterpart, thrombosis. They adhere to various subendothelial proteins, exposed either by injury or disease, and subsequently become activated by the thrombogenic surface or locally produced agonists. These activated platelets aggregate to form a platelet plug, release agonists which recruit more platelets to the growing thrombus, and provide a catalytic surface for thrombin generation and fibrin formation. These platelet-rich thrombi are responsible for the acute occlusion of stenotic vessels and ischemic injury to heart and brain. A range of anti-platelet drugs are currently used, both prophylactically and therapeutically, in regimens to manage thrombo-embolic disorders. These include inhibitors of the generation, or effects, of locally produced agonists; several large clinical trials have supported roles for cyclooxygenase inhibitors, which prevent thromboxane generation, and thienopyridine derivatives, which antagonize ADP receptors. Similarly intravenous αIIbβ3 antagonists have been shown to be effective anti-thrombotics, albeit in highly selective situations; in contrast, to date studies with their oral counterparts have been disappointing. Recent advances in understanding of platelet physiology have suggested several novel, if yet untested, targets for anti-platelet therapy. These include the thrombin receptor, the serotonin handling system, and the leptin receptor.

L10 ANSWER 13 OF 49 EMBASE

ACCESSION NUMBER: 2004032293 EMBASE
TITLE: Antiplatelet drugs in cardiovascular diseases.
AUTHOR: Weston C.; Rao U.
CORPORATE SOURCE: Dr. C. Weston, Department of Cardiology, Singleton Hospital, Sketty Lane, Swansea SA2 8QA, United Kingdom
SOURCE: International Journal of Clinical Practice, (2003) Vol. 57, No. 10, pp. 898-905. .
Refs: 55
ISSN: 1368-5031 CODEN: IJCPF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 29 Jan 2004
Last Updated on STN: 29 Jan 2004

AB Platelets play a key role in the pathogenesis of atherothrombotic conditions, e.g. acute coronary syndromes, cerebrovascular and peripheral vascular events. Antiplatelet agents interfere with platelet activation and aggregation and, as such, would be expected to modify the natural history of cardiovascular disease. In this review we explore the evidence to support the use of such drugs, singly or in combination, in a variety of situations characterised by thrombosis and summarise some of the concerns inherent in their use.

L10 ANSWER 14 OF 49 EMBASE
ACCESSION NUMBER: 2003291408 EMBASE
TITLE: Thrombosis in coronary artery disease: Its pathophysiology and control.
AUTHOR: Theroux P.
CORPORATE SOURCE: Dr. P. Theroux, Department of Medicine, Montreal Heart Institute, University of Montreal, 5000 Belanger East, Montreal, Que. H1T 1C8, Canada. theroux@ICM.Umontreal.ca
SOURCE: Dialogues in Cardiovascular Medicine, (2002) Vol. 7, No. 1, pp. 3-18. .
Refs: 49
ISSN: 1272-9949 CODEN: DCMIAV
COUNTRY: France
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2003
Last Updated on STN: 31 Jul 2003

AB Over the last two decades, converging observations on the close interactions between platelets and the coagulation system, and on the biology of the vessel wall, atherosclerosis, and inflammation, have established the role of intravascular thrombus formation as the immediate trigger for acute coronary syndromes. This progress in the understanding of the pathophysiological processes has been matched by the incremental success of treatment achieved by the introduction of aspirin and heparin, new antiplatelet agents (adenosine diphosphate [ADP] and GP IIb/IIIa [GP, glycoprotein] receptor antagonists), and new anticoagulants (low-molecular-weight heparins and direct thrombin inhibitors), and the judicious use of combined antiplatelet therapy and combined antiplatelet and anticoagulant therapy. This article reviews the mechanisms of thrombus formation, the current antithrombotic therapy, and the new antithrombotic therapy that is emerging at an accelerated pace, and the

rationale for their use.

L10 ANSWER 15 OF 49 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:100738 CAPLUS
DOCUMENT NUMBER: 144:198849
TITLE: Novel dosage form comprising modified-release and immediate-release active ingredients
INVENTOR(S): Vaya, Navin; Karan, Rajesh Singh; Sadanand, Sunil; Gupta, Vinod Kumar
PATENT ASSIGNEE(S): India
SOURCE: U.S. Pat. Appl. Publ., 49 pp., Cont.-in-part of U.S. Ser. No. 630,446.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006024365	A1	20060202	US 2005-134633	20050519
US 2004096499	A1	20040520	US 2003-630446	20030729

PRIORITY APPLN. INFO.:

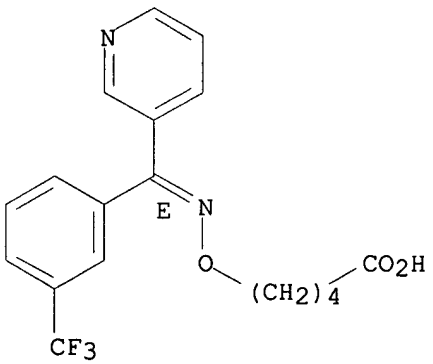
IN 2002-MU697	A	20020805
IN 2002-MU699	A	20020805
IN 2003-MU80	A	20030122
IN 2003-MU82	A	20030122
US 2003-630446	A2	20030729

AB A dosage form comprising of a high dose, high solubility active ingredient as modified release and a low dose active ingredient as immediate release where the weight ratio of immediate release active ingredient and modified release active ingredient is from 1:10 to 1:15000 and the weight of modified release active ingredient per unit is from 500 mg to 1500 mg; a process for preparing the dosage form. Tablets containing 10 mg sodium pravastatin and 1000 mg niacin were prepared The release of sodium pravastatin after 24 h was 67.7%, and the release of niacin after 1 h was 84.1%.

IT **110140-89-1, Ridogrel 113665-84-2, Clopidogrel**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(novel dosage form comprising modified-release and immediate-release active ingredients)

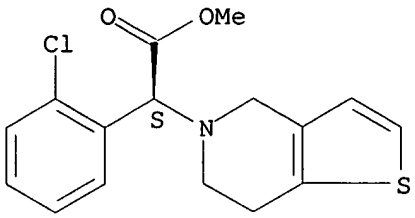
RN 110140-89-1 CAPLUS
CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



RN 113665-84-2 CAPLUS
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L10 ANSWER 16 OF 49 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:137173 CAPLUS
DOCUMENT NUMBER: 134:178396
TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
INVENTOR(S): Del Soldato, Piero
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001012584	A2	20010222	WO 2000-EP7225	20000727
WO 2001012584	A3	20020829		
W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2381409	AA	20010222	CA 2000-2381409	20000727
BR 2000013264	A	20020416	BR 2000-13264	20000727
EP 1252133	A2	20021030	EP 2000-953102	20000727
EP 1252133	B1	20050608		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003515526	T2	20030507	JP 2001-516885	20000727
NZ 516889	A	20041029	NZ 2000-516889	20000727
AU 781643	B2	20050602	AU 2000-65670	20000727
AT 297375	E	20050615	AT 2000-953102	20000727
EP 1593664	A1	20051109	EP 2005-104064	20000727
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, FI, RO, CY				
RU 2264383	C2	20051120	RU 2002-103509	20000727
ES 2243292	T3	20051201	ES 2000-953102	20000727
ZA 2002000628	A	20030423	ZA 2002-628	20020123
NO 2002000623	A	20020409	NO 2002-623	20020208
AU 2005202824	A1	20050721	AU 2005-202824	20050628

PRIORITY APPLN. INFO.:	IT 1999-MI1817	A	19990812
	EP 2000-953102	A3	20000727
	WO 2000-EP7225	W	20000727

OTHER SOURCE(S): MARPAT 134:178396

AB Compds. or their salts of general formula (I): A-B-N(O)s wherein: s is an integer equal to 1 or 2; A = R-T1-, wherein R is the drug radical and T1 = (CO)t or (X)t', wherein X = O, S, NR1c, R1c is H or a linear or branched alkyl or a free valence, t and t' are integers and equal to zero or 1, with the proviso that t = 1 when t' = 0; t = 0 when t' = 1; B = -TB -X2-O- wherein TB = (CO) when t = 0, TB = X when t' = 0, X being as above defined; X2, bivalent radical, is such that the precursor drug of A and the precursor of B meet resp. the pharmacol. tests described in the description. Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction

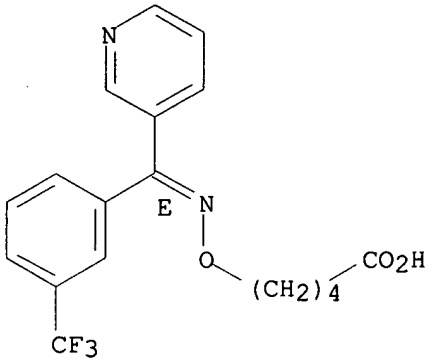
are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT **110140-89-1, Ridogrel**
RL: RCT (Reactant); RACT (Reactant or reagent)
(antithrombotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 110140-89-1 CAPLUS

CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

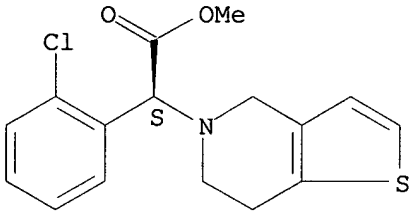


IT **113665-84-2, Clopidogrel**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 113665-84-2 CAPLUS

CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L10 ANSWER 17 OF 49 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:742057 CAPLUS

DOCUMENT NUMBER: 133:309791

TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction

INVENTOR(S): Del Soldato, Piero

PATENT ASSIGNEE(S): Nicox S.A., Fr.

SOURCE: PCT Int. Appl., 140 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061541	A2	20001019	WO 2000-EP3239	20000411
WO 2000061541	A3	20010927		

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID,

IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX,
NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

IT 1311923	B1	20020320	IT 1999-MI752		19990413
CA 2370425	AA	20001019	CA 2000-2370425		20000411
BR 2000009703	A	20020108	BR 2000-9703		20000411
EP 1169298	A2	20020109	EP 2000-926870		20000411
EP 1169298	B1	20060104			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY					
JP 2002541236	T2	20021203	JP 2000-610818		20000411
TR 200102928	T2	20021223	TR 2001-200102928		20000411
NZ 514270	A	20040227	NZ 2000-514270		20000411
RU 2237057	C2	20040927	RU 2001-127574		20000411
AU 777579	B2	20041021	AU 2000-45474		20000411
AT 315021	E	20060215	AT 2000-926870		20000411
ZA 2001008126	A	20030403	ZA 2001-8126		20011003
NO 2001004928	A	20011213	NO 2001-4928		20011010
US 6987120	B1	20060117	US 2001-926322		20011015
US 2006030605	A1	20060209	US 2005-234084		20050926
PRIORITY APPLN. INFO.:			IT 1999-MI752	A	19990413
			WO 2000-EP3239	W	20000411
			US 2001-926322	A3	20011015

OTHER SOURCE(S): MARPAT 133:309791

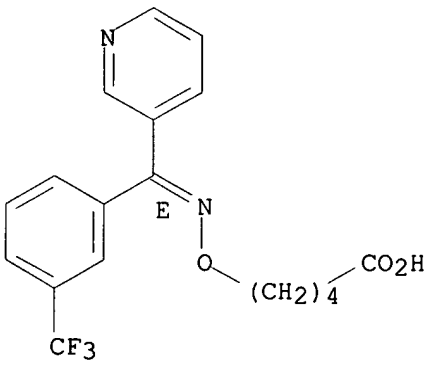
AB Synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction are disclosed. The precursors are such as to meet the pharmacol. test reported in the description.

IT **110140-89-1, Ridogrel**
RL: RCT (Reactant); RACT (Reactant or reagent)
(antithrombotic; synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 110140-89-1 CAPLUS

CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]amino]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.

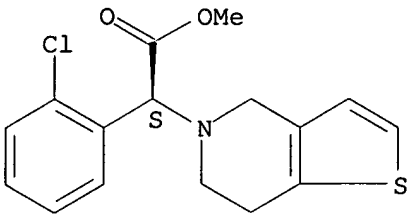


IT **113665-84-2, Clopidogrel**
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)

RN 113665-84-2 CAPLUS

CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L10 ANSWER 18 OF 49 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:742053 CAPLUS
DOCUMENT NUMBER: 133:310142
TITLE: Synthesis, activity and formulations of pharmaceutical compounds for treatment of oxidative stress and/or endothelial dysfunction
INVENTOR(S): Del Soldato, Piero
PATENT ASSIGNEE(S): Nicox S.A., Fr.
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000061537	A2	20001019	WO 2000-EP3234	20000411
WO 2000061537	A3	20010927		
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, DM, EE, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
IT 1311924	B1	20020320	IT 1999-MI753	19990413
CA 2370412	AA	20001019	CA 2000-2370412	20000411
BR 2000009702	A	20020108	BR 2000-9702	20000411
EP 1169294	A2	20020109	EP 2000-925203	20000411
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002541233	T2	20021203	JP 2000-610814	20000411
NZ 514267	A	20040625	NZ 2000-514267	20000411
RU 2237657	C2	20041010	RU 2001-127576	20000411
AU 778989	B2	20041223	AU 2000-44001	20000411
ZA 2001008127	A	20030103	ZA 2001-8127	20011003
NO 2001004927	A	20011213	NO 2001-4927	20011010
US 6869974	B1	20050322	US 2001-926326	20011015
US 2005261242	A1	20051124	US 2004-24857	20041230

PRIORITY APPLN. INFO.:
IT 1999-MI753 A 19990413
WO 2000-EP3234 W 20000411
US 2001-926326 A3 20011015

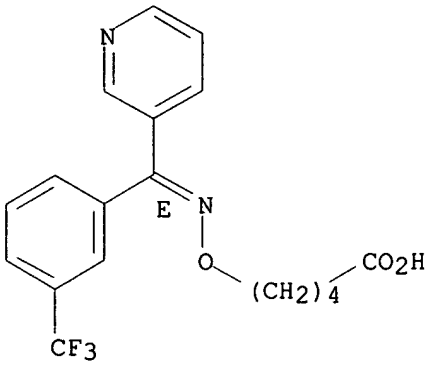
OTHER SOURCE(S): MARPAT 133:310142

AB Compds. A-B-C-N(O)s and A-C1[N(O)s]-B1 or their salts [s is an integer 1 or 2, preferably s = 2; A is the radical of a drug and is such as to meet the pharmacol. tests reported in the description; C and C1 are two bivalent radicals; the precursors of the radicals B and B1 are such as to meet the pharmacol. test reported in the description] were prepared for use as pharmaceuticals. Thus, (S,S)-N-acetyl-S-(6-methoxy-α-methyl-2-naphthalenylacetyl)cysteine 4-nitroxybutyl ester was prepared (NCX 2101) from naproxene and N-acetylcysteine in the first of 28 synthetic examples given. Pharmacol. test examples and tabular data are also given.

IT **110140-89-1, Ridogrel**
RL: RCT (Reactant); RACT (Reactant or reagent)
(drug precursor)
RN 110140-89-1 CAPLUS
CN Pentanoic acid, 5-[[(E)-[3-pyridinyl[3-(trifluoromethyl)phenyl]methylene]a

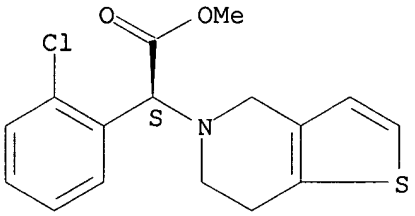
mino]oxy]- (9CI) (CA INDEX NAME)

Double bond geometry as shown.



IT **113665-84-2, Clopidogrel**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(synthesis, activity and formulations of pharmaceutical compds. for treatment of oxidative stress and/or endothelial dysfunction)
RN 113665-84-2 CAPLUS
CN Thieno[3,2-c]pyridine-5(4H)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (αS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L10 ANSWER 19 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001067234 EMBASE
TITLE: Antithrombotic agents in coronary artery disease.
AUTHOR: Cairns J.A.; Theroux P.; Lewis H.D. Jr.; Ezekowitz M.; Meade T.W.
CORPORATE SOURCE: Dr. J.A. Cairns, Faculty of Medicine, University of British Columbia, 317-2194 Health Sciences Mall, Vancouver, BC V6T 1Z3, Canada
SOURCE: Chest, (2001) Vol. 119, No. 1 SUPPL., pp. 228S-252S. .
Refs: 154
ISSN: 0012-3692 CODEN: CHETBF
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 015 Chest Diseases, Thoracic Surgery and Tuberculosis
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Mar 2001
Last Updated on STN: 16 Mar 2001
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 20 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1998030887 EMBASE
TITLE: New antiplatelet drugs.

AUTHOR: Joseph J.E.; Machin S.J.
CORPORATE SOURCE: Dr. J.E. Joseph, Univ. College London Medical School, Department of Haematology, The Haemostasis Research Unit, 98 Chenies Mews, London WC1E 6HX, United Kingdom
SOURCE: Blood Reviews, (1997) Vol. 11, No. 4, pp. 178-190. .
Refs: 107
ISSN: 0268-960X CODEN: BLOREB
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 5 Feb 1998
Last Updated on STN: 5 Feb 1998

AB Antiplatelet drugs are used in a wide range of disorders, either as sole agents or as adjuncts to other therapies. Aspirin has been shown to be clinically effective in a number of ischaemic conditions and has been in use for many years. The newer agents, ticlopidine and **clopidogrel** (which are thought to inhibit ADP-mediated platelet reactions) are also effective and may prove to be superior to aspirin in certain indications. However, ticlopidine in particular has a different spectrum of side-effects, which may eventually limit its widespread use. The Gp IIb/IIIa antagonists have been most extensively investigated in the acute corollary syndromes, and shown to significantly improve outcome. Most of these studies have utilized agents which need to be given parenterally, and subsequently oral compounds are currently being developed. A number of other antiplatelet drugs such as prostacyclin and its analogues, as well as thromboxane inhibitors have been studied over the years, but overall they have failed to demonstrate any real clinical advantage.

L10 ANSWER 21 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004179936 EMBASE
TITLE: [Clinical assessment of the preventive use of antiplatelet drugs].
VALORACION CLINICA DEL EMPLEO PREVENTIVO DE LA ANTIAGREGACION PLAQUETARIA.
AUTHOR: Lozano Almela M.L.; Vicente Garcia V.
CORPORATE SOURCE: M.L. Lozano, Centro Regional de Hemodonacion, C./ Ronda de Garay s/n, 30003 Murcia, Spain
SOURCE: Revista Clinica Espanola, (2004) Vol. 204, No. 2, pp. 106-108. .
Refs: 18
ISSN: 0014-2565 CODEN: RCESA5
COUNTRY: Spain
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
008 Neurology and Neurosurgery
015 Chest Diseases, Thoracic Surgery and Tuberculosis
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: Spanish
ENTRY DATE: Entered STN: 6 May 2004
Last Updated on STN: 6 May 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 22 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2003152138 EMBASE
TITLE: [Platelet inhibiting drugs: Old and new].
INHIBITEURS DU FONCTIONNEMENT PLAQUETTAIRE: ANCIENS ET NOUVEAUX.
AUTHOR: Lecompte T.
CORPORATE SOURCE: T. Lecompte, Universite Henri Poincare Nancy-1, CHU de

Nancy, Service d'Hematologle Biologique, Nancy, France
SOURCE: Tunisie Medicale, (2002) Vol. 80, No. 8 SUPPL., pp. 39-51.
Refs: 184
ISSN: 0041-4131 CODEN: TUMEAF
COUNTRY: Tunisia
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 025 Hematology
037 Drug Literature Index
LANGUAGE: French
SUMMARY LANGUAGE: English; French
ENTRY DATE: Entered STN: 1 May 2003
Last Updated on STN: 1 May 2003

AB Platelet inhibiting drugs are mainly used to prevent arterial thrombosis complicating atherosclerosis. Numerous clinical trials have delineated their clinical indications and precise guidelines are internationally available. The mechanism of action of aspirin is well understood: inhibition of platelet synthesis of thromboxane, and there is a pretty good relationship between pharmacology at the molecular and cellular levels and clinical results. The recently available drugs are the following. **Clopidogrel** is a thienopyridine, which irreversibly inhibits platelet activation by ADP interacting with the recently cloned P2Y12 receptor. There are also inhibitors of the fibrinogen binding to its platelet receptor, the glycoprotein IIb/IIIa complex, which is the key mechanism of platelet aggregation. These new drugs are widely used in patients with active coronary artery disease on top of aspirin.

L10 ANSWER 23 OF 49 EMBASE
ACCESSION NUMBER: 2002042055 EMBASE
TITLE: Antiplatelet therapy in acute coronary syndromes without persistent ST-segment elevation.
AUTHOR: Jain D.; Katus H.A.; Richardt G.
CORPORATE SOURCE: Dr. D. Jain, Medizinische Klinik II, Universitatsklinikum Lubeck, Medizinische Universitat Zu Lubeck, Ratzeburger Allee 160, D-23538 Lubeck, Germany.
drdeepakjain@hotmail.com
SOURCE: Cardiovascular Drugs and Therapy, (2001) Vol. 15, No. 5, pp. 423-436. .
Refs: 45
ISSN: 0920-3206 CODEN: CDTHET
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Feb 2002
Last Updated on STN: 14 Feb 2002

AB The treatment of ACS without persistent ST-segment elevation is evolving. Antiplatelet and antithrombin therapy forms the mainstay of medical management. The antiplatelet agents studied can be pharmacologically classified as GP IIb/IIIa receptor antagonists, ADP receptor antagonists, thromboxane inhibitors, and cyclo-oxgenase inhibitors. While aspirin, a cyclo-oxygenase inhibitor, is well entrenched in the treatment (and thus will not be reviewed here), other drugs have been subjects of intense study and large-scale clinical trials in the last decade. In this article we will explore the rationale of using antiplatelet agents, describe the platelet biology and mechanism of action of these drugs, narrate the major phase III trials, and attempt to draw conclusions from the clinical experience. Important trials which have been presented at principal international scientific meetings and which have not yet been published are also cited.

L10 ANSWER 24 OF 49 EMBASE
ACCESSION NUMBER: 95108661 EMBASE
DOCUMENT NUMBER: 1995108661

TITLE: Drugs for the prevention of coronary thrombosis: From an animal model to clinical trials.
AUTHOR: Folts J.D.
CORPORATE SOURCE: Cardiology Section, Clinical Science Center, University of Wisconsin, 600 Highland Avenue,Madison, WI 53792-3248, United States
SOURCE: Cardiovascular Drugs and Therapy, (1995) Vol. 9, No. 1 SUPPL. 1, pp. 31-43. .
ISSN: 0920-3206 CODEN: CDTHET
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 3 May 1995
Last Updated on STN: 3 May 1995

AB Platelets contribute to the profession of atherosclerotic disease and also to partial or complete thrombotic occlusion of stenosed human coronary or cerebral arteries. Thus, there is considerable interest in being able to measure in vivo or ex vivo platelet function or level of activity. Currently, platelet activity and the platelet inhibitory effect of drugs can be assessed ex vivo or in vitro by platelet aggregometry. There is also an experimental animal model (the cyclic flow, or Folts, model) for studying the interactions of platelets with damaged and stenosed arterial walls. This model was first used to show that aspirin can prevent coronary thrombosis in stenosed canine coronary arteries and is fairly predictive in determining which drugs are likely to inhibit platelet activity in vivo. It is also useful in identifying which drugs may be beneficial in ameliorating unstable angina and preventing coronary thrombosis. Studies with this model predict that aspirin, sulfinpyrazone, the monoclonal antibody 7E3 to the platelet glycoprotein GpIIb-IIIa fibrinogen receptor, arginine-glycine-aspartic acid peptide mimetics, or **clopidogrel** (an analogue of ticlopidine) would inhibit platelet-mediated thrombosis in patients with coronary or cerebral artery stenosis. The model also predicts that heparin or dipyridamole alone would not prevent platelet-mediated arterial thrombosis. Finally, studies with the cyclic model suggest that while serotonin receptor blockers, alpha-adrenergic blockade, or infusions of prostacyclin (or its analogue, Iloprost) would inhibit platelet activity, the resulting hypotension would severely limit the clinical usefulness of these compounds.

L10 ANSWER 25 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004316287 EMBASE
TITLE: Antiplatelet therapy, new and old.
AUTHOR: Puyo C.A.
CORPORATE SOURCE: Dr. C.A. Puyo, Dept. of Anesthesia/Critical Care, Beth Israel Deaconess Medical Center, One Deaconess Road, Boston, MA 02215, United States
SOURCE: International Anesthesiology Clinics, (2004) Vol. 42, No. 3, pp. 95-102. .
Refs: 24
ISSN: 0020-5907 CODEN: IACLAV
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Aug 2004
Last Updated on STN: 19 Aug 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 26 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001265124 EMBASE

TITLE: Aspirin in patients with coronary artery disease: Is it simply irresistible?.
AUTHOR: Nair G.V.; Davis C.J.; McKenzie M.E.; Lowry D.R.; Serebruany V.L.
CORPORATE SOURCE: Dr. V.L. Serebruany, Center for Thrombosis Research, Sinai Hospital, Schapiro Research Building R202, 2401 West Belvedere Avenue, Baltimore, MD 21215, United States. Heartdrug@aol.com
SOURCE: Journal of Thrombosis and Thrombolysis, (2001) Vol. 11, No. 2, pp. 117-126. .
Refs: 121
ISSN: 0929-5305 CODEN: JTTHFF
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 037 Drug Literature Index
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 2001
Last Updated on STN: 16 Aug 2001
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 27 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97379604 EMBASE
DOCUMENT NUMBER: 1997379604
TITLE: Advances in antiplatelet therapy in coronary artery disease: Importance of the platelet GPIIb/IIIa receptor.
AUTHOR: Timmis G.C.; Khurana S.
CORPORATE SOURCE: Dr. G.C. Timmis, Division of Cardiology, William Beaumont Hospital, 3601 W. Thirteen Mile Road, Royal Oak, MI 48073, United States
SOURCE: Journal of Interventional Cardiology, (1997) Vol. 10, No. 5, pp. 327-333. .
Refs: 29
ISSN: 0896-4327 CODEN: JICAF2
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jan 1998
Last Updated on STN: 15 Jan 1998

AB It is now widely agreed that platelets are intimately involved in and contribute to the pathogenesis of acute coronary thrombosis. Aspirin, a relatively weak inhibitor of platelet activation, saves lives when administered early after acute myocardial infarction and should be routinely used as lifelong therapy in patients with coronary atherosclerosis. Ticlopidine has a mechanism of action distinct from and additive to that of aspirin; it inhibits activation of platelets mediated by the agonist, adenosine diphosphate (ADP). The reduction in subacute coronary thrombosis attained by the use of combination therapy with aspirin and ticlopidine (for 2-4 weeks) after intracoronary stenting is further evidence of the role of platelets in mediating acute arterial thrombosis. Potent platelet agonists (like thrombin) can override the effect of aspirin and ticlopidine; therefore these agents are of limited efficacy. In contrast, inhibitors of the platelet glycoprotein (GP) IIb/IIIa receptor are potentially more potent inhibitors of adhesive platelet interaction and may therefore be effective in blocking adhesive platelet interactions irrespective of the activating agonist. The GPIIb/IIIa receptor mediates the bridging of platelets (platelet aggregation) via fibrinogen, thus allowing platelet to bind other platelets at the injured vessel wall. Antagonists of this receptor are thus capable of blocking the 'effector function' by acting at a step that

is downstream to platelet activation. By abrogating the final common pathway of platelet aggregation, antagonists of GPIIb/IIIa also affect the most proximal step in thrombin generation (that most efficiently occurs on the membrane surface provided by platelets). Accordingly, these agents can profoundly inhibit arterial thrombosis. The clinical use of the antibody fragment directed against the GPIIb/IIIa receptor (c7E3 Fab) has truly revolutionized the practice of interventional cardiology and has the potential to effectively treat heparin- resistant intracoronary thrombosis. Synthetic antagonists of fibrinogen binding to the GPIIb/IIIa receptor (the 'fibans') are currently under initial clinical testing.

L10 ANSWER 28 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 97352397 EMBASE
DOCUMENT NUMBER: 1997352397
TITLE: [Antiplatelet treatment].
TRAITEMENTS ANTIPLAQUETTAIRES.
AUTHOR: Zini J.-M.
CORPORATE SOURCE: J.-M. Zini, Service d'Angio-Hematologie, Hopital Lariboisiere, 2, Rue Ambroise-Pare, 75475 Paris Cedex 10, France
SOURCE: Medecine Therapeutique, (1997) Vol. 3, No. 8, pp. 651-657. .
Refs: 32
ISSN: 1264-6520 CODEN: METHFB
COUNTRY: France
DOCUMENT TYPE: Journal; (Short Survey)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: French
ENTRY DATE: Entered STN: 18 Dec 1997
Last Updated on STN: 18 Dec 1997

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 29 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 95261456 EMBASE
DOCUMENT NUMBER: 1995261456
TITLE: Clinical trials of primary and secondary prevention of thrombosis and restenosis.
AUTHOR: Vermylen J.
CORPORATE SOURCE: Center Molecular Vascular Biology, University of Leuven, Herestraat 49,B-3000 Leuven, Belgium
SOURCE: Thrombosis and Haemostasis, (1995) Vol. 74, No. 1, pp. 377-381. .
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 1995
Last Updated on STN: 19 Sep 1995

AB In the primary prevention of arterial disease, there may be a role for anti-oxidant vitamins and for oestrogen replacement therapy in postmenopausal women. For the secondary prevention of thrombotic complications of atherosclerosis, aspirin has proven efficacious in reducing both mortality and morbidity. Patients with ischaemic heart disease and moderately elevated serum cholesterol benefit from simvastatin administration. Heparin and oral anticoagulants are the mainstay in the primary and secondary prevention of venous thrombosis. More potent antithrombotic compounds, the direct thrombin inhibitors and the glycoprotein IIb-IIIa antagonists, are mainly being evaluated in emergency coronary medicine. Preliminary results are encouraging but haemorrhagic

problems need to be solved. The trend toward a decrease in late restenosis following coronary angioplasty using a IIb-IIIa antagonizing Fab fragment may prove to be a major therapeutic breakthrough.

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ACCESSION NUMBER: 92371555 EMBASE
DOCUMENT NUMBER: 1992371555
TITLE: Registry of multicenter clinical trials. Twelfth and thirteenth report- 1990-1991.
AUTHOR: Boissel J.P.; Bossard N.
CORPORATE SOURCE: Unite de Pharmacologie Clinique, Hopital Neuro-Cardiologique, 162 Avenue Lacassagne,69424 Lyon Cedex 03, France
SOURCE: Thrombosis and Haemostasis, (1992) Vol. 68, No. 6, pp. 752-778. .
ISSN: 0340-6245 CODEN: THHADQ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 009 Surgery
018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 1993
Last Updated on STN: 24 Jan 1993
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 31 OF 49 MEDLINE on STN

ACCESSION NUMBER: 96205088 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8647579
TITLE: [-Differential antithrombotic therapy in patients with low and high PTCA risk-].
Differenzierte antithrombotische Therapie bei Patienten mit niedrigem und hohem PTCA-Risiko.
AUTHOR: Silber S; Dorr R
CORPORATE SOURCE: Herzkatheterlabor der Kardiologischen Gemeinschaftspraxis, Klinik Dr. Muller, Munchen.
SOURCE: Herz, (1996 Feb) Vol. 21, No. 1, pp. 44-59. Ref: 213
Journal code: 7801231. ISSN: 0340-9937.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: German
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 5 Aug 1996
Last Updated on STN: 5 Aug 1996
Entered Medline: 19 Jul 1996

AB Acute coronary occlusion as well as restenosis still represent the major limitations of coronary interventions. Either event seems to be related to thrombus formation. The purpose of this overview is to summarize the current status of the usefulness of conventional and newer antithrombotic drugs regarding the prevention of acute occlusion and restenosis (excluding stents). ANTICOAGULATION: For ethical reasons, no placebo-controlled studies were conducted to prove the usefulness of heparin in preventing acute occlusions. The dosage mostly used is 10,000 U, although a relationship between dosage and complication rate has not been documented. A prolonged heparin infusion in patients with low risk and uncomplicated PTCA has no advantages. Restenosis is not influenced by prolonged infusion of heparin or administration of coumadin as well. Low molecular weight heparin is currently under investigation. Hirudin and hirulog have shown promising results with less acute occlusions; however, their therapeutic range must be considered. ANTIAGGREGATION: In controlled studies, ASA significantly reduced acute occlusions during PTCA when given in addition to heparin. Ticlopidin is as effective as ASA, but due to its side effects should only be administered when contraindications to ASA exist. ASA significantly reduced restenosis in only 1 of 4 studies with limited number of patients. Thromboxane inhibitors such as

ridogrel or **clopidogrel** showed promising initial results. Trapidil significantly reduced restenosis in 2 studies; quantitative stenosis analysis, however, was not performed. Inhibition of platelets by glycoprotein (GP) IIb/IIIa receptor antagonists represents an innovative therapeutic concept: numerous controlled trials have documented a significant reduction in cardiac ischemic events and therefore indirectly in restenosis rates. The recombinant monoclonal antibody c7E3 Fab seems to be more effective than the synthetic integrelin. Unfortunately, efficacy appears to be in direct relationship to the risk of bleeding complications. The clinical role of oral GP IIb/IIIa inhibitors has yet to be established. For patients with high risk PTCA, the use of hirudin instead of heparin as well as the addition of GP IIb/IIIa inhibitors should be considered.

L10 ANSWER 32 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2004430008 EMBASE
TITLE: Picotamide versus aspirin in diabetic patients with peripheral arterial disease: Has David defeated Goliath?.
AUTHOR: Gresele P.; Migliacci R.
CORPORATE SOURCE: grespa@unipg.it
SOURCE: European Heart Journal, (2004) Vol. 25, No. 20, pp. 1769-1771. .
Refs: 16
ISSN: 0195-668X CODEN: EHJODF
PUBLISHER IDENT.: S 0195-668X(04)00576-7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Editorial
FILE SEGMENT: 003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Oct 2004
Last Updated on STN: 21 Oct 2004
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 33 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2001170829 EMBASE
TITLE: Future directions in antithrombotic therapy: Emphasis on venous thromboembolism.
AUTHOR: Axelrod D.A.; Wakefield T.W.
CORPORATE SOURCE: Dr. D.A. Axelrod, 6312 Medical Science Bldg 1, 1150 W Medical Center Dr., Ann Arbor, MI 48109, United States
SOURCE: Journal of the American College of Surgeons, (2001) Vol. 192, No. 5, pp. 641-651. .
Refs: 61
ISSN: 1072-7515 CODEN: JACSEX
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 23 May 2001
Last Updated on STN: 23 May 2001
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 34 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1999325044 EMBASE
TITLE: Glycoprotein IIb/IIIa receptor antagonists. Clinical pharmacology in cardiovascular diseases of aging.
AUTHOR: Sebastian M.; Makkar R.
CORPORATE SOURCE: Dr. R. Makkar, Cardiovascular Intervention Center, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, United States. rajmakkar@aol.com
SOURCE: Drugs and Aging, (1999) Vol. 15, No. 3, pp. 207-218. .
Refs: 75

ISSN: 1170-229X CODEN: DRAGE6
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
020 Gerontology and Geriatrics
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Sep 1999
Last Updated on STN: 30 Sep 1999

AB The aging process is accompanied by a series of anatomical and physiological cardiovascular changes, including a generalised loss of vascular compliance, neuroendocrine alterations and endothelial dysfunction. Superimposed on this, there is an age-related increase in common cardiovascular disorders, such that the majority of deaths and much disability in older populations are caused by coronary artery disease. Most acute vascular events are mediated by thrombosis in which the formation of platelet aggregates forms an integral part. Research over recent years has led to the characterisation of the platelet glycoprotein (GP) IIb/IIIa receptor as the ultimate mechanism by which activated platelets cross-link by binding fibrinogen and other ligands. This knowledge has resulted in novel pharmacological strategies targeting this receptor which have proven to be potent inhibitors of thrombosis. The prototype drug, abciximab, is a chimeric monoclonal antibody directed against GP IIb/IIIa. Synthesis of new drugs has followed, based on the identification of the molecular sequences to which GP IIb/IIIa is attracted. This includes the emergence of oral agents which can be used for long term therapy. Clinical trials with these agents in the setting of percutaneous coronary interventions and unstable ischaemic syndromes have demonstrated a beneficial effect on thrombosis-related end-points. Trials of GP IIb/IIIa antagonists for direct percutaneous transluminal coronary angioplasty (PTCA) in acute myocardial infarction have also shown benefit, while their use in combination with fibrinolytic drugs is currently being evaluated. Other potential indications including neurovascular disease and primary haematological disorders are also being explored.

L10 ANSWER 35 OF 49 EMBASE
ACCESSION NUMBER: 1998010349 EMBASE
TITLE: Antiplatelet therapy: Do the new platelet inhibitors add significantly to the clinical benefits of aspirin?.
AUTHOR: Theroux P.
CORPORATE SOURCE: Dr. P. Theroux, Montreal Heart Institute, 5000 Belanger St. E., Montreal, Que. H1T 1C8, Canada
SOURCE: American Heart Journal, (1997) Vol. 134, No. 5 II, pp. S62-S70. .
Refs: 53
ISSN: 0002-8703 CODEN: AHJOA2
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Feb 1998
Last Updated on STN: 2 Feb 1998

AB The inhibitors of the platelet membrane glycoprotein IIb/IIIa show considerable promise as antiplatelet agents. These drugs are easily titrated when administered intravenously and are associated with less frequent and serious bleeding than initially feared. They add significant benefit to that attributable to aspirin in preventing the complications associated with coronary angioplasty. Pilot studies have suggested that benefits could also be realized in acute myocardial infarction and

unstable angina. The most effective means of administering these agents, their relative efficacy, and the consequences of long-term modulation of the glycoprotein IIb/IIIa receptor by oral agents are challenging areas for clinical investigation.

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ACCESSION NUMBER: 97265715 EMBASE
DOCUMENT NUMBER: 1997265715
TITLE: Unmet therapeutic needs in the management of acute ischemia.
AUTHOR: White H.D.
CORPORATE SOURCE: H.D. White, Cardiology Department, Green Lane Hospital, Auckland 1030, New Zealand
SOURCE: American Journal of Cardiology, (1997) Vol. 80, No. 4 A, pp. 2B-10B. .
Refs: 62
ISSN: 0002-9149 CODEN: AJCDAG
PUBLISHER IDENT.: S 0002-9149(97)00571-7
COUNTRY: United States
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 1997
Last Updated on STN: 2 Oct 1997

AB Unstable angina and myocardial infarction (MI) continue to present a major challenge in clinical management. These acute ischemic coronary syndromes (AICS) are a spectrum of clinical presentations of the same pathophysiologic mechanism: thrombus formation superimposed on atherosclerotic plaque disruption or erosion. Current approaches to the management of AICS, which include beth interventional and pharmacologic therapy, have been introduced to clinical practice during the past 20 years, and most of them have demonstrated efficacy in clinical studies. A common inadequacy of current therapies, however, is the lack of significant inhibition of platelet aggregation-the crucial event in the formation of coronary thrombi and the pathogenesis of AICS. The final common pathway to platelet aggregation is the activation of the platelet glycoprotein (GP) IIb- IIIa receptor, which allows the cross-linking of adjacent platelets by the adhesive plasma proteins fibrinogen and von Willebrand's factor. The emergence of the GP IIb-IIIa receptor as a potential treatment target has led to the development of several inhibitors of its function. The inhibitors most advanced in clinical development are the chimeric monoclonal antibody abciximab (ReoPro) and the cyclic peptide eptifibetide (INTEGRILIN). In phase III clinical trials, both abciximab and eptifibatide have been shown to reduce the incidence of cardiac events in patients at risk for abrupt vessel closure after coronary angioplasty. Inhibition of the GP IIb-IIIa receptor is the most promising novel approach to the treatment of unstable angina and MI, and it may soon be an indispensable component of the management of patients with AICS.

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ACCESSION NUMBER: 1999334918 EMBASE
TITLE: [Thrombocyte receptors: Current views and therapeutic possibilities].
TROMBOCYTENRECEPTOREN: HUIDIGE INZICHTEN EN BEHANDELINGSMOGELIJKHEDEN.
AUTHOR: Peters R.J.G.; Moons A.H.M.; Buller H.R.
CORPORATE SOURCE: Dr. R.J.G. Peters, Academisch Medisch Centrum, Universiteit van Amsterdam, Postbus 22.660, 1100 DD Amsterdam, Netherlands
SOURCE: Nederlands Tijdschrift voor Geneeskunde, (25 Sep 1999) Vol. 143, No. 39, pp. 1952-1957. .
Refs: 24

ISSN: 0028-2162 CODEN: NETJAN
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: Dutch
SUMMARY LANGUAGE: English; Dutch
ENTRY DATE: Entered STN: 7 Oct 1999
Last Updated on STN: 7 Oct 1999

AB In the action of thrombocytes during stemming of a bleeding after damage to a blood vessel, receptors on the thrombocyte membrane play an important part. - Adhesion of platelets takes place via specific binding of receptors; the main binding is that of glycoprotein (Gp) Ib to Von Willebrand factor which is synthetized by endothelial cells. - Activation of thrombocytes is stimulated by adhesion and by agonists. Weak agonists, through production of thromboxane A2 and release of agonists from granules cause a self-fortifying process of thrombocyte stimulation; strong agonists (like thrombin) lead also to activation of Gp IIb/IlIa receptors. - Aggregation of thrombocytes occurs after activation of Gp IIb/IIIa receptors. During stimulation, a change of shape occurs which enables binding to suitable plasma proteins of which the main one is fibrinogen. - Knowledge of thrombocyte receptors enhances the insight into the prognosis and efficacy of certain treatments in diseases in which platelet aggregation is pivotal. - Of the six categories of antiplatelet drugs, antagonists of Gp IIb/IIIa receptors are the most potent. In clinical trials good results have been obtained in patients with coronary disease of the intravenously administered form added to acetylsalicylic acid.

L10 ANSWER 38 OF 49 EMBASE
ACCESSION NUMBER: 1999228936 EMBASE
TITLE: Pharmacological basis of antiplatelet drugs in acute myocardial infarction: Focus on triflusal.
AUTHOR: Dalla-Volta S.
CORPORATE SOURCE: S. Dalla-Volta, Divisione di Cardiologia, Policlinico Universitario, Via Giustiniani 2, 35128 Padova, Italy
SOURCE: European Heart Journal, Supplement, (1999) Vol. 1, No. F, pp. F7-F11. .
Refs: 35
ISSN: 1520-765X CODEN: EHJSFT
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Jul 1999
Last Updated on STN: 15 Jul 1999

AB The vital role of antiplatelet treatment in patients with acute coronary syndromes is now well established. Antiplatelet agents may differ in their mechanism of action and this may have clinical implications. The new anti-aggregatory agent triflusal has been shown to inhibit effectively platelet-mediated thrombosis. Triflusal (1) produces specific irreversible inhibition of platelet cyclo-oxygenase activity, thereby reducing platelet thromboxane A2 formation; (2) inhibits cAMP phosphodiesterase and increases platelet cAMP levels, thereby inhibiting Ca2+-dependent platelet aggregation; (3) stimulates nitric oxide generation and inhibits superoxide anion production in human neutrophils. At therapeutic concentrations, triflusal is selective for platelet cyclo-oxygenase, lacks activity against vascular endothelial cyclo-oxygenase and has no effect on prostacyclin biosynthesis. Its main metabolite, 3-hydroxy-4-trifluoro-methylbenzoic acid (HTB), has a prolonged plasma half-life (35 h) and is pharmacologically active, stimulating cAMP production in platelets. In keeping with its pharmacological profile, triflusal is an effective antiplatelet agent. It

has a clinical efficacy comparable to aspirin in the treatment of thromboembolic coronary and cerebrovascular disease, but is associated with a lower risk of haemorrhagic complications.

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ACCESSION NUMBER: 1998291586 EMBASE
TITLE: The clinical utility of antiplatelet drugs.
AUTHOR: Messmore H.L. Jr.; Wehrmacher W.H.; Coyne E.
CORPORATE SOURCE: Dr. H.L. Messmore Jr., Loyola University Medical Center, 2160 S. First Avenue, Maywood, IL 60153, United States
SOURCE: Cardiovascular Reviews and Reports, (1998) Vol. 19, No. 8, pp. 21-32. .
Refs: 42
ISSN: 0197-3118 CODEN: CRRPD4
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 15 Oct 1998
Last Updated on STN: 15 Oct 1998

AB It is now necessary for every physician to be cognizant of the value of antiplatelet drugs in the management of atherothrombotic disease of the vascular system. Five antiplatelet drugs are now approved or recommended for clinical use, but aspirin and heparin, given separately or together, are the antiplatelet drugs of choice for 80% of the clinical indications. Ticlopidine (Ticlid®), abciximab (ReoPro®), and dipyridamole (Persantine®) are approved for only limited uses at this time. Improved physician awareness of the value of these drugs for certain common indications will lead to improved quality and length of life for many patients who are now undertreated.

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ACCESSION NUMBER: 96140296 EMBASE
DOCUMENT NUMBER: 1996140296
TITLE: Endothelial dysfunction in preeclampsia. Part II: Reducing the adverse consequences of endothelial cell dysfunction in preeclampsia; Therapeutic perspectives.
AUTHOR: Dekker G.A.; Van Geijn H.P.
CORPORATE SOURCE: Division of Maternal-Fetal Medicine, Department Obstetrics and Gynecology, Free University Hospital, De Boelelaan 1117,NL-1081 HV Amsterdam, Netherlands
SOURCE: Journal of Perinatal Medicine, (1996) Vol. 24, No. 2, pp. 119-139. .
ISSN: 0300-5577 CODEN: JPEMAO
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 010 Obstetrics and Gynecology
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English; German; French
ENTRY DATE: Entered STN: 29 May 1996
Last Updated on STN: 29 May 1996

AB Next to low-dose Aspirin there appear to be several new and promising pharmacologie approaches for reducing the adverse consequences of endothelial cell dysfunction in preeclampsia. Among these are selective thromboxane-A2 synthetase and/or thromboxane-A2 receptor antagonists, stable prostacyclin analogues, selective S (erotonin)2-receptor blockers, nitrovasodilators, glycoprotein IIb/IIIa antagonists, hirudin, and

ticlopidine. Early-onset preeclampsia appears to be associated with certain disorders that are likely to provoke an arterial thrombotic process by impairing the normal endothelial cell-platelet interactions. Especially heterozygous hyperhomocyxteinemia, protein S deficiency and anticardiolipin antibodies appear to be fairly common. The management of these 3 separate disease entities will be discussed.

L10 ANSWER 41 OF 49 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1997:146751 BIOSIS
DOCUMENT NUMBER: PREV199799445954
TITLE: Platelet inhibition with oral antagonists to thromboxane, serotonin, and ADP reduces neointimal proliferation in a hypercholesterolemia canine coronary angioplasty model.
AUTHOR(S): Anderson, H. V.; McNatt, J.; Lateef, M.; Martin, C.; Clubb, F.; Buja, L. M.; Willerson, J. T.
CORPORATE SOURCE: Univ. Tex. Med. Sch., Houston, TX, USA
SOURCE: Journal of the American College of Cardiology, (1997) Vol. 29, No. 2 SUPPL. A, pp. 51A.
Meeting Info.: 46th Annual Scientific Session of the American College of Cardiology. Anaheim, California, USA. March 16-19, 1997.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Apr 1997
Last Updated on STN: 2 Apr 1997

L10 ANSWER 42 OF 49 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

ACCESSION NUMBER: 1995:145013 BIOSIS
DOCUMENT NUMBER: PREV199598159313
TITLE: Combined Treatment with 3 Antiplatelet Agents Reduces Neointimal Proliferation in Canine Coronary Arteries After Angioplasty.
AUTHOR(S): Anderson, H. Vernon [Reprint author]; McNatt, Janice; Cui, Kexin; Mower, Lowell; Martin, Cory; Maffrand, Jean Pierre; Declerck, Fred; Clubb, Fred; Buja, L. Maximilian; Willerson, James T.
CORPORATE SOURCE: Univ. Texas Med. Sch., Houston, TX, USA
SOURCE: Journal of the American College of Cardiology, (1995) Vol. 0, No. SPEC. ISSUE, pp. 225A-226A.
Meeting Info.: 44th Annual Scientific Session of the American College of Cardiology. New Orleans, Louisiana, USA. March 19-22, 1995.
CODEN: JACCDI. ISSN: 0735-1097.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Apr 1995
Last Updated on STN: 4 Apr 1995

L10 ANSWER 43 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1998146470 EMBASE
TITLE: [New antithrombotic treatment of acute coronary artery syndromes].
NIEUWE ANTITROMBNOTISCHE BEHANDELING VAN ACUTE KRANSSLAGADERSYNDROMEN.
AUTHOR: Budts W.; Van de Werf F.
CORPORATE SOURCE: F. Van de Werf, Dienst Interne Geneeskunde, Afdeling Cardiologie, Universitaire Ziekenhuizen, Leuven, Belgium
SOURCE: Tijdschrift voor Geneeskunde, (1 May 1998) Vol. 54, No. 9, pp. 616-621. .
Refs: 26
ISSN: 0371-683X CODEN: TGEKBW
COUNTRY: Belgium
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
025 Hematology
037 Drug Literature Index
LANGUAGE: Dutch
SUMMARY LANGUAGE: Dutch
ENTRY DATE: Entered STN: 20 May 1998
Last Updated on STN: 20 May 1998
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 44 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 97244987 EMBASE
DOCUMENT NUMBER: 1997244987
TITLE: [New antithrombotic drugs in development].
NEUE ANTITHROMBOTISCHE MEDIKAMENTE.
AUTHOR: Greinacher A.
CORPORATE SOURCE: Prof. Dr. A. Greinacher, Inst. fur Immunol./Transfusionsmed., Ernst-Moritz-Arndt-Universitat, DZ/Sauerbruchstrasse, D-17487 Greifswald, Germany
SOURCE: Internist, (1997) Vol. 38, No. 7, pp. 680-687. .
Refs: 41
ISSN: 0020-9554 CODEN: INTEAG
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: German
SUMMARY LANGUAGE: German
ENTRY DATE: Entered STN: 25 Sep 1997
Last Updated on STN: 25 Sep 1997
DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 45 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 96315587 EMBASE
DOCUMENT NUMBER: 1996315587
TITLE: Importance of a medical treatment in mesenteric vein thrombosis (MVT).
AUTHOR: Moriau M.; Azerad M.-A.
CORPORATE SOURCE: Hematology Division, Hemostasis and Thrombosis Unit, University of Louvain,1200 Brussels, Belgium
SOURCE: Acta Gastro-Enterologica Belgica, (1996) Vol. 59, No. 2, pp. 146-149. .
ISSN: 0001-5644 CODEN: AGEBAX
COUNTRY: Belgium
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 006 Internal Medicine
009 Surgery
037 Drug Literature Index
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 25 Nov 1996
Last Updated on STN: 25 Nov 1996
AB Mesenteric vein thrombosis (MVT) and particularly superior mesenteric vein thrombosis (SMVT) can induce 5 to 15 percents of mesenteric and intestinal infarctions in a small and large bowels. The thrombotic process can be idiopathic or consecutive to inherited or acquired thrombophilic states. The clinical diagnosis of this event remains difficult and requires always specific imaging investigations to treat as soon as possible. Its evolution and mortality rate are quite different than these observed in arterial mesenteric ischemic accident. Medical treatment with thrombolytic, anticoagulant, antiplatelet and antispasmodic agents, initiated promptly after precocious diagnosis is able not only to prevent surgical procedure but also to reduce significantly the mortality and recurrence rate of this venous thrombotic event.

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ACCESSION NUMBER: 96288737 EMBASE
DOCUMENT NUMBER: 1996288737
TITLE: Antiplatelet and anticoagulant use after myocardial infarction.
AUTHOR: Almony G.T.; Lefkovits J.; Topol E.J.
CORPORATE SOURCE: Department of Cardiology, Cleveland Clinic Foundation, One Clinic Center,Cleveland, OH 44195, United States
SOURCE: Clinical Cardiology, (1996) Vol. 19, No. 5, pp. 357-365. .
ISSN: 0160-9289 CODEN: CLCADC
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Oct 1996
Last Updated on STN: 28 Oct 1996

AB Coronary thrombosis leading to myocardial infarction is a complex process involving the interaction of the arterial wall, the coagulation cascade, and platelets. Increased understanding of the molecular biology of thrombosis has prompted an evolution in antithrombotic therapy, from the early use of warfarin following myocardial infarction to agents targeting specific receptors or modulators in the thrombotic process. The complexity of thrombosis allows for numerous sites of pharmacologic intervention; the multiple pathways leading to platelet aggregation and thrombin formation provide the opportunity for combined therapies. This review presents the current clinical data on antiplatelet, anticoagulant, and specific antithrombin therapies following myocardial infarction.

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ACCESSION NUMBER: 94041698 EMBASE
DOCUMENT NUMBER: 1994041698
TITLE: Antiplatelet agents in the prevention of diabetic vascular complications.
AUTHOR: Patrono C.; Davi G.
CORPORATE SOURCE: Universita Studi G. D'Annunzio, Facolta di Medicina e Chirurgia, Via dei Vestini 31,Chieti 66013, Italy
SOURCE: Diabetes/Metabolism Reviews, (1993) Vol. 9, No. 3, pp. 177-188. .
ISSN: 0742-4221 CODEN: DMREEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
037 Drug Literature Index
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Mar 1994
Last Updated on STN: 6 Mar 1994

DATA NOT AVAILABLE FOR THIS ACCESSION NUMBER

L10 ANSWER 48 OF 49 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 90192513 EMBASE
DOCUMENT NUMBER: 1990192513
TITLE: [New Developments in anti-platelet therapy]. NOUVELLES THERAPEUTIQUES ANTIAGREGANTES.
AUTHOR: Maffrand J.P.
CORPORATE SOURCE: SANOFI Recherche, 195 Route D'Espagne, 31000 Toulouse,, France
SOURCE: Sang Thrombose Vaisseaux, (1990) Vol. 2, No. 4, pp. 175-177. .
ISSN: 0999-7385 CODEN: STVAEY
COUNTRY: France
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AB BACKGROUND: Platelet-derived growth factors help stimulate the neointimal proliferation of restenosis after coronary interventions. Reducing platelet accumulation at treated sites may attenuate restenosis. We tested this hypothesis by inducing repetitive platelet aggregation at coronary angioplasty sites in dogs and measuring subsequent neointima formation. METHODS AND RESULTS: Cholesterol-sensitive dogs (n=74) received either 4% cholesterol-enriched diets for >8 months (n=29), creating visible atheromas, or normal canine diets (n=45). A coronary balloon angioplasty cyclic flow variation (CFV) model was used. One group of control dogs (group 1, n=8) had angioplasty with no arterial constriction applied and no drug treatment. Three other groups had arterial constrictors applied to provoke CFVs: group 2 (n=28) received no drug therapy, group 3 (n=18) received oral aspirin alone, and group 4 (n=20) received 3 oral antiplatelet agents: **ridogrel**, ketanserin, and **clopidogrel** (R+K+C) to simultaneously inhibit the thromboxane A(2), serotonin, and ADP pathways of platelet aggregation, respectively. Bleeding times were moderately prolonged in the aspirin-treated group (124+/-9 seconds after 3 weeks versus 76+/-6 seconds at baseline, P<0.01) and greatly prolonged on R+K+C (>600 versus 104+/-5 seconds, P<0.001). The frequency and severity of CFVs were inversely related to the degree of platelet inhibition and prolongation of bleeding times, as was sudden death due to acute thrombotic coronary occlusion. Quantitative histology at 8 weeks revealed increased intima-to-media ratio with CFVs: 0.89+/-0.14 in the untreated group 2 versus 0.11+/-0.04 in the control group (P<0.001). Intima-to-media ratio was significantly reduced with antiplatelet treatment (0.27+/-0.05 with aspirin treatment and 0.20+/-0.05 with R+K+C treatment, respectively, P<0.001). Cholesterol feeding did not appear to influence results. CONCLUSIONS: Repetitive platelet accumulation at coronary angioplasty sites caused enhanced neointimal proliferation by 8 weeks. Oral inhibitors of platelet aggregation attenuated platelet function, prolonged bleeding times, reduced or prevented cyclic flows and abrupt thrombotic occlusions, and thereby inhibited neointimal proliferation. Platelet inhibition should continue to receive attention in efforts to reduce restenosis after coronary interventions.

BRIGHAM AND WOMEN'S HOSPITAL
A Teaching Affiliate of Harvard Medical School

FDA Approval of Drug-coated Stents to have Major Impact on Future of Cardiovascular Care

Boston - April 2003, Harvard Medical School affiliate Brigham and Women's Hospital - Researchers at three Boston hospitals - Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH) - who jointly coordinated and were the only participating New England centers for the national clinical trial of drug coated stents, hailed today's decision by the Food and Drug Administration (**FDA**) to approve these devices for widespread use in cardiovascular care.

Currently, metal stents are implanted to prevent blood vessels on the heart from closing after angioplasty, a procedure in which a balloon catheter is inserted to clear blocked arteries. It is estimated that more than 20 percent of angioplasty patients suffer **restenosis**, a condition in which the arteries do not heal well around the device, and eventually narrow or close-off again, necessitating repeat angioplasty or heart bypass surgery.

Today's **FDA** approval clears the way for the device to be made widely available in the United States. The **FDA** advisory panel unanimously recommended the device be **approved** last October after reviewing the study's results.

"The study looked at a wide variety of subsets of patients whom we treat with stents, including both conventional patients as well as those with diabetes, hypertension, long segments of narrowing, and others at severe risk for **restenosis**," said Igor Palacios, MD, Director, Cardiac Catheterization Laboratory at MGH. "Remarkably, the advantages of using the drug coated stent were seen across the board, in essentially all types of patients. Since most patients appear to benefit, the implications of this new therapy are profound, now that this technology will be available for routine use."

The stents that were studied are coated with a drug that arrests cell growth and stops scar tissue from forming within arteries that have been opened. The stents release the drug slowly over the first few weeks after insertion, when scarring is most likely to occur.

"When we tested the drug coated devices versus the plain metal version on patients, the results were very compelling. In approximately 95 percent of patients receiving the drug-coated stents, **restenosis** was prevented," said Campbell Rogers, MD, Director, Cardiac Catheterization Laboratory at BWH. "Drug-coated stents will be the new standard of cardiovascular care essentially immediately upon their release."

"With more than one million patients undergoing angioplasty and stenting annually, the patient population that this change will impact immediately is immense," said Joseph Carrozza, MD, Director of Interventional Cardiology at BIDMC. "The stent will dramatically improve the overall quality of care by reducing the likelihood a patient will have to undergo repeated invasive procedures. We anticipate the devices will be widely available within the next several weeks."

The national clinical trial, which was funded by Cordis Corporation, a unit of Johnson & Johnson Company, and the maker of the stent, followed 1,058 patients for eight months. The trial involved MGH, BWH, BIDMC, and 50 other medical facilities around the country. In the study, the clinical outcomes of 533 patients who received the drug-coated stent were compared to 525 patients who were treated with the metal stent.

In addition to their positions at each respective hospital, the three physicians involved in this study are also on the teaching staff of Harvard Medical School.

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ATHEROGENICS, INC.

• INVESTOR RELATIONS •

PRESS RELEASE 2001

AtheroGenics Reports Phase II Clinical Results For AGI-1067 In Post-Angioplasty Restenosis

Preliminary Analysis Indicates Dose-related Increase in Luminal Diameter at Six Months

ATLANTA, GA - May 21 - AtheroGenics, Inc. (Nasdaq: AGIX), an emerging pharmaceutical company focused on the treatment of chronic inflammatory diseases, today announced encouraging preliminary results of a Phase II clinical trial of AGI-1067, an oral agent for the treatment of **restenosis** after percutaneous coronary intervention (PCI), a procedure commonly known as "angioplasty".

An analysis of the results indicated that six months after angioplasty, the blood vessels of patients who received AGI-1067 had greater luminal diameters of their coronary arteries than those patients who received placebo. This improvement showed a statistically significant dose response. At the highest dose of AGI-1067, the increase in the size of the target blood vessel was similar to that achieved with probucol, the active control drug in CART-1 (Canadian Antioxidant **Restenosis** Trial), which has been shown in previous clinical studies to reduce **restenosis** rates significantly following angioplasty without stent deployment.

An unexpected apparent benefit of drug treatment affected the use of the method typically specified for analyzing primary endpoint in a **restenosis** study. Because of this apparent early drug benefit on coronary arteries, AtheroGenics has not **yet** determined whether CART-1 met its primary statistical endpoint as pre-specified in the protocol. A full analysis of the safety and efficacy data is underway and expected to be announced later this year.

There were **no** deaths or increase in the incidence of serious adverse events when comparing AGI-1067 to placebo. In CART-1, an important safety issue was whether AGI-1067 would cause a prolongation of the QTc interval, which is an electrophysiological abnormality of the heart. The study showed that AGI-1067 did not cause QTc prolongation. Conversely, probucol did cause QTc

prolongation in a statistically significant proportion of patients.

"CART-1 results confirm and extend the findings from the MVP clinical study of probucol for the treatment of **restenosis**, which were published in the New England Journal of Medicine," said Jean-Claude Tardif, MD, FRCPC, Director of Clinical Research at the Montreal Heart Institute and Principal Investigator of CART-1. "In CART-1, AGI-1067 appears to exhibit the benefit of probucol therapy without the potential shortcomings associated with QTc prolongation."

This multi-center, randomized, double-blinded, placebo-controlled study, known as CART-1, comprised 305 men and women who were treated by angioplasty, with or without intracoronary stenting. The study was conducted at five clinical sites in Canada, led by the Montreal Heart Institute and included four other major cardiovascular teaching hospitals. Prior to angioplasty, patients were randomized to one of five treatment arms: AGI-1067 doses of either 70 mg, 140 mg or 280 mg, once daily, probucol 500 mg twice daily or placebo.

"This clinical study represents an important achievement in AtheroGenics' clinical development program," said Russell M. Medford, M.D., Ph.D., President and Chief Executive Officer of AtheroGenics. "We are all very excited about these statistically significant results, which are the first demonstration of biological activity of AGI-1067 in patients."

CART-1 study investigators have submitted abstracts for presentation at the American Heart Association meeting in November 2001.

Schering-Plough Corporation has exclusive worldwide rights to develop and commercialize AGI-1067 and is funding all development and commercialization costs. Under the license agreement, AtheroGenics receives upfront and milestone payments totaling as much as $189 million, plus royalties on sales of any approved product covered by the license agreement.

To date, **there** are **no** approved drugs for the prevention or treatment of **restenosis** after angioplasty. **Restenosis** is the re-narrowing or reclosure of coronary arteries after angioplasty in patients with coronary artery disease. Angioplasty procedures have been proven to be very effective in opening clogged arteries and have become widely used by cardiologists. More than one million patients around the world underwent the procedure last year. Unfortunately, angioplasty induces an inflammatory response that contributes to **restenosis** within approximately six months in up to 40% of the patients who undergo the procedure.

About AtheroGenics
AtheroGenics is focused on the discovery, development and commercialization of novel drugs for the treatment of chronic inflammatory diseases such as heart disease (atherosclerosis), rheumatoid arthritis and asthma. The company recently commenced enrollment in a Phase I clinical study for AGIX-4207, Aecond v-protectant clinical candidate, a novel oral agent being developed for the treatment of the signs and symptoms of rheumatoid arthritis. For more information about AtheroGenics, please visit www.atherogenics.com.

About Schering-Plough
Schering-Plough Corporation of Kenilworth, N.J., is a research-based company engaged in the discovery, development, manufacturing and marketing pharmaceutical products worldwide. wide.

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projections about our future results of operations or our financial condition, our collaborative efforts with Schering-Plough Corporation, the development of our product candidates, anticipated trends in our business, and other risks that could cause actual results to differ materially. These risks are discussed in AtheroGenics' Securities and Exchange Commission filings, including the company's registration statement on Form S-1, Registration **No**. *333-31140, filed with the SEC, and including but not limited to the risks discussed in AtheroGenics' Form 10-K for fiscal 2000, and our most recent Quarterly Report on Form 10-Q for the quarter ended March 31, 2001, all of which are incorporated by reference into this press release. These documents may also be examined at public reference facilities maintained by the SEC or, to the extent filed via EDGAR, accessed through the SEC's web site (http://www.sec.gov).*

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Windhover Information Inc.
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Hijacking the Restenosis Market

(*Start-Up: Windhover's Review of Emerging Medical Ventures*, November 2001 page 24)

Innovative device companies have always had to contend with the Sword of Damocles of unexpected technological obsolescence hanging over their heads. But for would-be developers of interventional devices for the prevention of **restenosis**, the sword is dangling perilously close. At the European Society of Cardiology (ESC) meeting in Stockholm in early September, principal investigator Dr. Marie-Claude Morice (Institut Hospitalier Jacques Cartier) stunned an audience of cardiologists with the positive results of the RAVEL trial, which demonstrated efficacy against **restenosis** of Johnson & Johnson's BX Velocity stent coated with the immunosuppressive drug rapamycin (alternate name sirolimus) patented by Wyeth-Ayerst.

In a trial of 238 patients in Europe and Latin America, Morice reported that the control group receiving a bare stent experienced typical **restenosis** rates of 26%. But in the group treated with the rapamycin-coated stent, **no restenosis** occurred at all—at least for the six months of the trial. The usually reserved audience of cardiologists at the ESC conference spontaneously broke into applause at the news.

Such enthusiasm is not unwarranted. For twenty years, **restenosis** has been an omnipresent problem for interventional cardiology, compromising outcomes and limiting the number of patients that could benefit from interventional procedures instead of coronary artery bypass graft surgery. Cardiologists refer many types of patients directly to surgery because of their increased risk of developing **restenosis**. Were it not for **restenosis**, they would be able to treat more patients in a minimally invasive manner, they argue.

Until November 2000, when Novoste and J&J's Cordis division both received FDA approvals for intravascular radiation (brachytherapy) catheters for the treatment of in-

stent **restenosis**, there were **no effective** options for **restenosis** prevention. Although such a large market representing a completely unmet need had for years attracted dozens of development efforts in pharmaceuticals, devices, and combinations of the two, until last year, none had been successful.

Drug coated stent developers investigated and rejected many projects as they searched for the right device coating that wouldn't invoke an inflammatory response and that could also hold and elute the right dosage of an anti-**restenosis** drug. Concurrent with drug coated stent efforts, perhaps a half-dozen companies had been formed over the past decade, to try to control the aberrant healing response that characterizes **restenosis**. They tried a variety of approaches, with ultrasonic devices (Pharmasonics, Angiosonics), cold therapy (Cryovascular); light-activated drugs (Pharmacyclics) and x-ray energy (Xoft microTube), among others.

Given all the difficulties that stent manufacturers had faced, these companies believed they had as good a chance as anyone of getting first to market with an **effective** anti-**restenosis** device. Now, however, in the aftermath of the RAVEL trial results, for this group of young, privately funded non-stent device companies, the landscape has changed overnight. Companies have been forced to re-evaluate their business strategies in the face of a competing technology that could drastically reduce their target markets.

The success of drug coated stents at preventing **restenosis** would mean that the market for ancillary, catheter-based technologies would be much smaller than the estimates in companies' original business plans. Drug coated stents possess a tremendous advantage over adjunctive technologies; interventional cardiologists already use stents in 80% of their revascularization procedures. Now, the challenge for the non-stent **restenosis** companies is to prove that their devices show efficacy in some indication that doesn't lend itself to stenting.

Granted, it is very early to place bets on drug-coated stents. RAVEL was a relatively small study with strict inclusion-exclusion criteria. Since the trial looked at results for six months only, long-term data is unavailable.

Questions that remain unanswered are whether the therapy eliminates or simply delays **restenosis**, and whether or not there are any harmful long-term effects on vessel integrity from the use of the immunosuppressive or cytotoxic drugs. Meanwhile, the risk that drug-coated stents will ultimately prove to be broadly efficacious has small companies re-evaluating their markets and business strategies.

For some companies it is a question of getting out of the coronary business altogether, and applying technologies to other therapeutic areas like cancer, the strategy of Xoft microTube. Others, like Pharmasonics and Omnisonics are adopting a "go with the flow" philosophy, with the message that they offer adjunctive technologies that have the potential to complement or enhance the performance of drug-coated stents. Meanwhile, they hope to amass the clinical data that could enable them to excel in standalone applications.

Still others, like brachytherapy manufacturers Novoste and Guidant, believe that because of the variability of patients and lesions types, there will be **no** single "magic bullet" against **restenosis**. These companies believe there will be a substantial number of

coronary cases for which their approach will be more **effective** than drug coated stents, for example, in patients with diabetes, smaller vessels, calcified lesions, vessels too small to stent, complicated anatomy, or long lesions. Alternative applications in neurovascular or the peripheral vasculature offer additional markets to some companies. Economics will also play a part in the need for alternative technologies.

For many early-stage companies, it will be difficult to get the financing they need for mustering the clinical data that supports their products superior performance. Moreover, in the absence of long-term data on drug-eluting stents, the niche strategy is a weak one. The risk thus exists that alternative technologies will simply be shut out of the coronary **restenosis** business.

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Stent and Deliver

(*Start-Up: Windhover's Review of Emerging Medical Ventures*, June 2000 page 34)

Restenosis-the tendency of vessels to reocclude in the months following balloon angioplasty-is often described as an "annuity" for interventional cardiologists, although the physicians themselves describe it as the bane of their existence. The desire to eliminate **restenosis** propelled the rapid adoption of stents, from their early clinical uses in 1994 to a penetration rate today of just about 70% of all angioplasty procedures.

Unfortunately, however, stents don't go far enough to prevent **restenosis**-anywhere from 10% to 40% of patients will develop **restenosis** within six months of revascularization procedures-and they frequently result in a new, man-made and **difficult**-to-**treat** kind of **restenosis** known as in-stent **restenosis**. Device developers are thus putting serious development effort into enhanced stents that can carry and deliver **drugs** to combat **restenosis** locally.

The idea is simple and intuitive, but a lot of unanswered questions remain. For one thing, it is **difficult** to know which drug to use to attack **restenosis**, a disease influenced by multiple mechanisms. There are technological unknowns as well concerning which coating materials work best, and which strategies to use to release **drugs** from the stent.

The field began with stent manufacturers looking into stent coatings to reduce the thrombogenicity of the implanted devices. A handful of private companies in Europe has been very active in developing antithrombotic surface coatings. InFlow Dynamics AG, for example, has experimented with gold-coated stents. Biotronik GMBH & Co. has developed a hard, impermeable silicon carbide coating that acts as a semiconductor that prevents the electronic transfer of fibrinogen on the metallic surface of the stent. Carmeda AB was perhaps the first company to make the leap from antithrombogenic surface coating to antithrombotic drug. The Swedish company has developed a coating that covalently

bonds the anticoagulant heparin to metallic stents. Its technology underlies a heparin-coated stent manufactured by Cordis Corp., which received FDA approval earlier this year.

Biocompatibles set out to prove the mettle of its coating independently of adjunctive **drugs**. Its *BiodivYsio* stent, which the company launched in Europe in 1998, is coated with phosphorylcholine, a phospholipid that predominates in cell membranes. The company has subsequently launched a drug delivery stent that is being marketed as an empty stent to be filled by cardiologists in the hospital. SurModics has a device surface coating that is versatile and can coat devices with **drugs** under gentle conditions.

A fundamental problem underlying the development of **restenosis**-drug-eluting stents is that no single drug stands out as an effective treatment for the disease. Neither the etiology nor the respective contributions of multiple mechanisms to **restenosis** are completely known. Pharmaceutical companies have tested and abandoned a number of potential anti-restenotic agents-anticoagulants, platelet aggregation inhibitors, growth receptor antagonists, anti-fibrotic **drugs**, and cholesterol-lowering **drugs**. Perhaps the **drugs** acted too specifically for this multi-factorial disease. Or, perhaps some of the **drugs** would work if delivered locally for a sustained period of time. Drug developers are watching stent developments carefully to see if coated stents might revive stalled **restenosis** programs.

Meanwhile, device companies are working with a wide range of agents. Johnson and Johnson is working on a *ReoPro*-coated stent as well as a stent coated with the immunosuppressive drug rapamycin. InFlow is looking into antithrombotic hirudin for its stent coating. One company is also investigating the use of the corticosteroid, prednisolone. Cook Group says that it evaluated as many as 20 **drugs** before settling on paclitaxel as its lead candidate, and it has other coated stent programs in research. Cook was the first company to enter a drug-coated stent into clinical trials, earlier this year. Boston Scientific will soon follow, with its version of a paclitaxel-coated stent.

Several companies hope that the way to knock out multi-mechanism **restenosis** is with a multi-action drug. So believes an unnamed device company that is coating stents with SmithKline Beecham's tranilast, which is in Phase III clinical trials for **restenosis**. NitroMed Inc. is another proponent of the multi-action drug. Its intellectual property gives it an almost exclusive ability to coat a medical device with nitric oxide, a natural anticoagulant, a vasodilator, a neurotransmitter, and a mediator of immune system functions.

Others are acting on the philosophy that in biology, it is easier to promote a process than to top it. CardioVasc hopes to accelerate the process of endothelialization with a peptide mimetic that recruits endothelial cells to the surface of a stent.

All these drug-device combinations are merely promising ideas, for now. The proof is in the clinical trials, which are just beginning. In **restenosis**, animal models are particularly poor predictors of efficacy in humans. And companies have a lot of problems to solve, including the compatibility of coatings with blood and the immune system and with the **drugs** that they are trying to deliver. Plus, uncertainty surrounds the efficacy of the **drugs** themselves.

Still, successful products will enter a $2 billion worldwide market, one in which interventional cardiologists are eager for therapies that will eliminate the scourge of **restenosis**.